DEX-0209 CF

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/79286 A2

(51) International Patent Classification[7]: C07K 14/47

(21) International Application Number: PCT/US01/12164

(22) International Filing Date: 12 April 2001 (12.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

09/551,621	17 April 2000 (17.04.2000)	US
09/590,751	8 June 2000 (08.06.2000)	US
09/604,287	22 June 2000 (22.06.2000)	US
09/620,405	20 July 2000 (20.07.2000)	US

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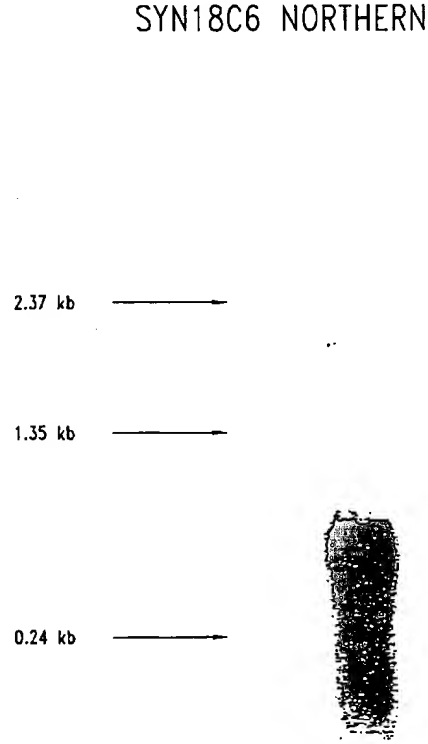
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF BREAST CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as breast cancer, are disclosed. Compositions may comprise one or more breast tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a breast tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as breast cancer. Diagnostic methods based on detecting a breast tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF BREAST CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as breast cancer. The invention is more specifically related to polypeptides comprising at least a portion of a breast tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in compositions for prevention and treatment of breast cancer, and for the diagnosis and monitoring of such cancers.

BACKGROUND OF THE INVENTION

Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast cancer are one in eight.

No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. *See, e.g.*, Porter-Jordan and Lippman, *Breast Cancer 8*:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for the treatment and diagnosis of breast cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as breast cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a breast tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489; (b) variants of a sequence recited in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487 and 488, and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a breast tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic compositions, or vaccines for prophylactic or therapeutic use are provided. Such compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a breast tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as

described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that

comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins. Exemplary fusion proteins according to the present invention comprise a first amino acid portion and a second amino acid portion wherein the first amino acid portion includes 9 or more contiguous amino acids from mammaglobin as depicted by amino acids 1-93 of SEQ ID NO: 493; wherein the second amino acid portion includes 9 or more contiguous amino acids from B726P as depicted by SEQ ID NO: 475, SEQ ID NO: 469, or SEQ ID NO: 176; and wherein the first amino acid portion is connected to either the amino terminal or carboxy-terminal end of the second amino acid portion.

Still further embodiments of the present invention provide fusion proteins

wherein said first amino acid portion is selected from the group consisting of IDELKECFLNQTDETLSNVE (amino acids 59-78 of SEQ ID NO: 493); TTNAIDELKECFLNQ (amino acids 55-69 of SEQ ID NO: 493); SQHCYAGSGCPLLENVISKTI (amino acids 13-33 of SEQ ID NO: 493); EYKELLQEFIDDNATTNAID (amino acids 41-60 of SEQ ID NO: 493); KLLMVLMLA (amino acids 2-10 of SEQ ID NO: 493); QEFIDDNATTNAI (amino acids 47-59 of SEQ ID NO: 493); and LKECFLNQTDETL (amino acids 62-74 of SEQ ID NO: 493).

Alternative embodiments provide fusion proteins wherein the second amino acid portion includes 9 or more contiguous amino acids encoded by (1) the combined upstream and downstream open reading frame (ORF) of B726P as depicted in SEQ ID NO: 475; (2) the upstream ORF of B726P as depicted in from SEQ ID NO:

469; and (3) the downstream ORF of B726P as depicted in SEQ ID NO: 176. Fusion proteins according to the present invention may also comprise a second amino acid portion that includes 9 or more contiguous amino acids from the amino acid sequence depicted by amino acids 1-129 of SEQ ID NO: 475. Still additional exemplary fusion proteins are depicted herein by SEQ ID NO: 493; SEQ ID NO: 494; and SEQ ID NO: 495.

Fusion proteins are provided wherein the mammaglobin amino acid portion is connected to the amino-terminus of the B726P amino acid portion while other fusion proteins are provided wherein the mammaglobin amino acid portion is connected to the carboxy-terminus of the B726P amino acid portion. The connection between the mammaglobin amino acid portion and the B726P portion may be a covalent bond. Additionally, a stretch of amino acids either unrelated or related to either mammaglobin and/or B726P may be incorporated between or either amino- or carboxy-terminal to either the mammaglobin and/or B726P amino acid portion.

The present invention also provides isolated polynucleotides that encode any of the fusion proteins that are specifically disclosed herein as well as those fusion proteins that may be accomplished with routine experimentation by the ordinarily skilled artisan.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with breast cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological

sample with T cells that specifically react with a breast tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a breast tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a breast tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a

cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be breast cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Fig. 1 shows the results of a Northern blot of the clone SYN18C6 (SEQ ID NO: 40).

SEQ ID NO: 1 is the determined cDNA sequence of JBT2.

SEQ ID NO: 2 is the determined cDNA sequence of JBT6.

SEQ ID NO: 3 is the determined cDNA sequence of JBT7.

SEQ ID NO: 4 is the determined cDNA sequence of JBT10.

SEQ ID NO: 5 is the determined cDNA sequence of JBT13.

SEQ ID NO: 6 is the determined cDNA sequence of JBT14.

SEQ ID NO: 7 is the determined cDNA sequence of JBT15.

SEQ ID NO: 8 is the determined cDNA sequence of JBT16.

SEQ ID NO: 9 is the determined cDNA sequence of JBT17.

SEQ ID NO: 10 is the determined cDNA sequence of JBT22.

SEQ ID NO: 11 is the determined cDNA sequence of JBT25.

SEQ ID NO: 12 is the determined cDNA sequence of JBT28.

SEQ ID NO: 13 is the determined cDNA sequence of JBT32.

SEQ ID NO: 14 is the determined cDNA sequence of JBT33.

SEQ ID NO: 15 is the determined cDNA sequence of JBT34.

SEQ ID NO: 16 is the determined cDNA sequence of JBT36.

SEQ ID NO: 17 is the determined cDNA sequence of JBT37.

SEQ ID NO: 18 is the determined cDNA sequence of JBT51.

SEQ ID NO: 19 is the determined cDNA sequence of JBTT1.

SEQ ID NO: 20 is the determined cDNA sequence of JBTT7.

SEQ ID NO: 21 is the determined cDNA sequence of JBTT11.

SEQ ID NO: 22 is the determined cDNA sequence of JBTT14.

SEQ ID NO: 23 is the determined cDNA sequence of JBTT18.

SEQ ID NO: 24 is the determined cDNA sequence of JBTT19.

SEQ ID NO: 25 is the determined cDNA sequence of JBTT20.

SEQ ID NO: 26 is the determined cDNA sequence of JBTT21.

SEQ ID NO: 27 is the determined cDNA sequence of JBTT22.

SEQ ID NO: 28 is the determined cDNA sequence of JBTT28.

SEQ ID NO: 29 is the determined cDNA sequence of JBTT29.

SEQ ID NO: 30 is the determined cDNA sequence of JBTT33.

SEQ ID NO: 31 is the determined cDNA sequence of JBTT37.

SEQ ID NO: 32 is the determined cDNA sequence of JBTT38.

SEQ ID NO: 33 is the determined cDNA sequence of JBTT47.

SEQ ID NO: 34 is the determined cDNA sequence of JBTT48.

SEQ ID NO: 35 is the determined cDNA sequence of JBTT50.

SEQ ID NO: 36 is the determined cDNA sequence of JBTT51.

SEQ ID NO: 37 is the determined cDNA sequence of JBTT52.

SEQ ID NO: 38 is the determined cDNA sequence of JBTT54.

SEQ ID NO: 39 is the determined cDNA sequence of SYN17F4.

SEQ ID NO: 40 is the determined cDNA sequence of SYN18C6 (also known as B709P).

SEQ ID NO: 41 is the determined cDNA sequence of SYN19A2.

SEQ ID NO: 42 is the determined cDNA sequence of SYN19C8.

SEQ ID NO: 43 is the determined cDNA sequence of SYN20A12.

SEQ ID NO: 44 is the determined cDNA sequence of SYN20G6.

SEQ ID NO: 45 is the determined cDNA sequence of SYN20G6-2.

SEQ ID NO: 46 is the determined cDNA sequence of SYN21B9.

SEQ ID NO: 47 is the determined cDNA sequence of SYN21B9-2.

SEQ ID NO: 48 is the determined cDNA sequence of SYN21C10.

SEQ ID NO: 49 is the determined cDNA sequence of SYN21G10.

SEQ ID NO: 50 is the determined cDNA sequence of SYN21G10-2.

SEQ ID NO: 51 is the determined cDNA sequence of SYN21G11.

SEQ ID NO: 52 is the determined cDNA sequence of SYN21G11-2.

SEQ ID NO: 53 is the determined cDNA sequence of SYN21H8.

SEQ ID NO: 54 is the determined cDNA sequence of SYN22A10.

SEQ ID NO: 55 is the determined cDNA sequence of SYN22A10-2.

SEQ ID NO: 56 is the determined cDNA sequence of SYN22A12.

SEQ ID NO: 57 is the determined cDNA sequence of SYN22A2.

SEQ ID NO: 58 is the determined cDNA sequence of SYN22B4.

SEQ ID NO: 59 is the determined cDNA sequence of SYN22C2.

SEQ ID NO: 60 is the determined cDNA sequence of SYN22E10.

SEQ ID NO: 61 is the determined cDNA sequence of SYN22F2.

SEQ ID NO: 62 is a predicted amino acid sequence for SYN18C6 (also known as B709P).

SEQ ID NO: 63 is the determined cDNA sequence of B723P.

SEQ ID NO: 64 is the determined cDNA sequence for B724P.

SEQ ID NO: 65 is the determined cDNA sequence of B770P.

SEQ ID NO: 66 is the determined cDNA sequence of B716P.

SEQ ID NO: 67 is the determined cDNA sequence of B725P.

SEQ ID NO: 68 is the determined cDNA sequence of B717P.

SEQ ID NO: 69 is the determined cDNA sequence of B771P.

SEQ ID NO: 70 is the determined cDNA sequence of B722P.

SEQ ID NO: 71 is the determined cDNA sequence of B726P.

SEQ ID NO: 72 is the determined cDNA sequence of B727P.

SEQ ID NO: 73 is the determined cDNA sequence of B728P.

SEQ ID NO: 74-87 are the determined cDNA sequences of isolated clones which show homology to known sequences.

SEQ ID NO: 88 is the determined cDNA sequence of 13053.

SEQ ID NO: 89 is the determined cDNA sequence of 13057.

SEQ ID NO: 90 is the determined cDNA sequence of 13059.

SEQ ID NO: 91 is the determined cDNA sequence of 13065.

SEQ ID NO: 92 is the determined cDNA sequence of 13067.

SEQ ID NO: 93 is the determined cDNA sequence of 13068.

SEQ ID NO: 94 is the determined cDNA sequence of 13071.

SEQ ID NO: 95 is the determined cDNA sequence of 13072.

SEQ ID NO: 96 is the determined cDNA sequence of 13073.

SEQ ID NO: 97 is the determined cDNA sequence of 13075.

SEQ ID NO: 98 is the determined cDNA sequence of 13078.

SEQ ID NO: 99 is the determined cDNA sequence of 13079.

SEQ ID NO: 100 is the determined cDNA sequence of 13081.

SEQ ID NO: 101 is the determined cDNA sequence of 13082.

SEQ ID NO: 102 is the determined cDNA sequence of 13092.

SEQ ID NO: 103 is the determined cDNA sequence of 13097.

SEQ ID NO: 104 is the determined cDNA sequence of 13101.

SEQ ID NO: 105 is the determined cDNA sequence of 13102.

SEQ ID NO: 106 is the determined cDNA sequence of 13119.

SEQ ID NO: 107 is the determined cDNA sequence of 13131.

SEQ ID NO: 108 is the determined cDNA sequence of 13133.

SEQ ID NO: 109 is the determined cDNA sequence of 13135.

SEQ ID NO: 110 is the determined cDNA sequence of 13139.

SEQ ID NO: 111 is the determined cDNA sequence of 13140.

SEQ ID NO: 112 is the determined cDNA sequence of 13146.

SEQ ID NO: 113 is the determined cDNA sequence of 13147.

SEQ ID NO: 114 is the determined cDNA sequence of 13148.

SEQ ID NO: 115 is the determined cDNA sequence of 13149.

SEQ ID NO: 116 is the determined cDNA sequence of 13151.

SEQ ID NO: 117 is the determined cDNA sequence of 13051

SEQ ID NO: 118 is the determined cDNA sequence of 13052

SEQ ID NO: 119 is the determined cDNA sequence of 13055

SEQ ID NO: 120 is the determined cDNA sequence of 13058

SEQ ID NO: 121 is the determined cDNA sequence of 13062
SEQ ID NO: 122 is the determined cDNA sequence of 13064
SEQ ID NO: 123 is the determined cDNA sequence of 13080
SEQ ID NO: 124 is the determined cDNA sequence of 13093
SEQ ID NO: 125 is the determined cDNA sequence of 13094
SEQ ID NO: 126 is the determined cDNA sequence of 13095
SEQ ID NO: 127 is the determined cDNA sequence of 13096
SEQ ID NO: 128 is the determined cDNA sequence of 13099
SEQ ID NO: 129 is the determined cDNA sequence of 13100
SEQ ID NO: 130 is the determined cDNA sequence of 13103
SEQ ID NO: 131 is the determined cDNA sequence of 13106
SEQ ID NO: 132 is the determined cDNA sequence of 13107
SEQ ID NO: 133 is the determined cDNA sequence of 13108
SEQ ID NO: 134 is the determined cDNA sequence of 13121
SEQ ID NO: 135 is the determined cDNA sequence of 13126
SEQ ID NO: 136 is the determined cDNA sequence of 13129
SEQ ID NO: 137 is the determined cDNA sequence of 13130
SEQ ID NO: 138 is the determined cDNA sequence of 13134
SEQ ID NO: 139 is the determined cDNA sequence of 13141
SEQ ID NO: 140 is the determined cDNA sequence of 13142
SEQ ID NO: 141 is the determined cDNA sequence of 14376
SEQ ID NO: 142 is the determined cDNA sequence of 14377
SEQ ID NO: 143 is the determined cDNA sequence of 14383
SEQ ID NO: 144 is the determined cDNA sequence of 14384
SEQ ID NO: 145 is the determined cDNA sequence of 14387
SEQ ID NO: 146 is the determined cDNA sequence of 14392
SEQ ID NO: 147 is the determined cDNA sequence of 14394
SEQ ID NO: 148 is the determined cDNA sequence of 14398
SEQ ID NO: 149 is the determined cDNA sequence of 14401
SEQ ID NO: 150 is the determined cDNA sequence of 14402
SEQ ID NO: 151 is the determined cDNA sequence of 14405
SEQ ID NO: 152 is the determined cDNA sequence of 14409
SEQ ID NO: 153 is the determined cDNA sequence of 14412

SEQ ID NO: 154 is the determined cDNA sequence of 14414

SEQ ID NO: 155 is the determined cDNA sequence of 14415

SEQ ID NO: 156 is the determined cDNA sequence of 14416

SEQ ID NO: 157 is the determined cDNA sequence of 14419

SEQ ID NO: 158 is the determined cDNA sequence of 14426

SEQ ID NO: 159 is the determined cDNA sequence of 14427

SEQ ID NO: 160 is the determined cDNA sequence of 14375

SEQ ID NO: 161 is the determined cDNA sequence of 14378

SEQ ID NO: 162 is the determined cDNA sequence of 14379

SEQ ID NO: 163 is the determined cDNA sequence of 14380

SEQ ID NO: 164 is the determined cDNA sequence of 14381

SEQ ID NO: 165 is the determined cDNA sequence of 14382

SEQ ID NO: 166 is the determined cDNA sequence of 14388

SEQ ID NO: 167 is the determined cDNA sequence of 14399

SEQ ID NO: 168 is the determined cDNA sequence of 14406

SEQ ID NO: 169 is the determined cDNA sequence of 14407

SEQ ID NO: 170 is the determined cDNA sequence of 14408

SEQ ID NO: 171 is the determined cDNA sequence of 14417

SEQ ID NO: 172 is the determined cDNA sequence of 14418

SEQ ID NO: 173 is the determined cDNA sequence of 14423

SEQ ID NO: 174 is the determined cDNA sequence of 14424

SEQ ID NO: 175 is the determined cDNA sequence of B726P-20

SEQ ID NO: 176 is the predicted amino acid sequence of B726P-20

SEQ ID NO: 177 is a PCR primer

SEQ ID NO: 178 is the determined cDNA sequence of B726P-74

SEQ ID NO: 179 is the predicted amino acid sequence of B726P-74

SEQ ID NO: 180 is the determined cDNA sequence of B726P-79

SEQ ID NO: 181 is the predicted amino acid sequence of B726P-79

SEQ ID NO: 182 is the determined cDNA sequence of 19439.1, showing homology to the mammaglobin gene

SEQ ID NO: 183 is the determined cDNA sequence of 19407.1, showing homology to the human keratin gene

SEQ ID NO: 184 is the determined cDNA sequence of 19428.1, showing homology to human chromosome 17 clone

SEQ ID NO: 185 is the determined cDNA sequence of B808P (19408), showing no significant homology to any known gene

SEQ ID NO: 186 is the determined cDNA sequence of 19460.1, showing no significant homology to any known gene

SEQ ID NO: 187 is the determined cDNA sequence of 19419.1, showing homology to Ig kappa light chain

SEQ ID NO: 188 is the determined cDNA sequence of 19411.1, showing homology to human alpha-1 collagen

SEQ ID NO: 189 is the determined cDNA sequence of 19420.1, showing homology to mus musculus proteinase-3

SEQ ID NO: 190 is the determined cDNA sequence of 19432.1, showing homology to human high motility group box

SEQ ID NO: 191 is the determined cDNA sequence of 19412.1, showing homology to the human plasminogen activator gene

SEQ ID NO: 192 is the determined cDNA sequence of 19415.1, showing homology to mitogen activated protein kinase

SEQ ID NO: 193 is the determined cDNA sequence of 19409.1, showing homology to the chondroitin sulfate proteoglycan protein

SEQ ID NO: 194 is the determined cDNA sequence of 19406.1, showing no significant homology to any known gene

SEQ ID NO: 195 is the determined cDNA sequence of 19421.1, showing homology to human fibronectin

SEQ ID NO: 196 is the determined cDNA sequence of 19426.1, showing homology to the retinoic acid receptor responder 3

SEQ ID NO: 197 is the determined cDNA sequence of 19425.1, showing homology to MyD88 mRNA

SEQ ID NO: 198 is the determined cDNA sequence of 19424.1, showing homology to peptide transporter (TAP-1) mRNA

SEQ ID NO: 199 is the determined cDNA sequence of 19429.1, showing no significant homology to any known gene

SEQ ID NO: 200 is the determined cDNA sequence of 19435.1, showing homology to human polymorphic epithelial mucin

SEQ ID NO: 201 is the determined cDNA sequence of B813P (19434.1), showing homology to human GATA-3 transcription factor

SEQ ID NO: 202 is the determined cDNA sequence of 19461.1, showing homology to the human AP-2 gene

SEQ ID NO: 203 is the determined cDNA sequence of 19450.1, showing homology to DNA binding regulatory factor

SEQ ID NO: 204 is the determined cDNA sequence of 19451.1, showing homology to Na/H exchange regulatory co-factor

SEQ ID NO: 205 is the determined cDNA sequence of 19462.1, showing no significant homology to any known gene

SEQ ID NO: 206 is the determined cDNA sequence of 19455.1, showing homology to human mRNA for histone HAS.Z

SEQ ID NO: 207 is the determined cDNA sequence of 19459.1, showing homology to PAC clone 179N16

SEQ ID NO: 208 is the determined cDNA sequence of 19464.1, showing no significant homology to any known gene

SEQ ID NO: 209 is the determined cDNA sequence of 19414.1, showing homology to lipophilin B

SEQ ID NO: 210 is the determined cDNA sequence of 19413.1, showing homology to chromosome 17 clone hRPK.209_J_20

SEQ ID NO: 211 is the determined cDNA sequence of 19416.1, showing no significant homology to any known gene

SEQ ID NO: 212 is the determined cDNA sequence of 19437.1, showing homology to human clone 24976 mRNA

SEQ ID NO: 213 is the determined cDNA sequence of 19449.1, showing homology to mouse DNA for PG-M core protein

SEQ ID NO: 214 is the determined cDNA sequence of 19446.1, showing no significant homology to any known gene

SEQ ID NO: 215 is the determined cDNA sequence of 19452.1, showing no significant homology to any known gene

SEQ ID NO: 216 is the determined cDNA sequence of 19483.1, showing no significant homology to any known gene

SEQ ID NO: 217 is the determined cDNA sequence of 19526.1, showing homology to human lipophilin C

SEQ ID NO: 218 is the determined cDNA sequence of 19484.1, showing homology to the secreted cement gland protein XAG-2

SEQ ID NO: 219 is the determined cDNA sequence of 19470.1, showing no significant homology to any known gene

SEQ ID NO: 220 is the determined cDNA sequence of 19469.1, showing homology to the human HLA-DM gene

SEQ ID NO: 221 is the determined cDNA sequence of 19482.1, showing homology to the human pS2 protein gene

SEQ ID NO: 222 is the determined cDNA sequence of B805P (19468.1), showing no significant homology to any known gene

SEQ ID NO: 223 is the determined cDNA sequence of 19467.1, showing homology to human thrombospondin mRNA

SEQ ID NO: 224 is the determined cDNA sequence of 19498.1, showing homology to the CDC2 gene involved in cell cycle control

SEQ ID NO: 225 is the determined cDNA sequence of 19506.1, showing homology to human cDNA for TREB protein

SEQ ID NO: 226 is the determined cDNA sequence of B806P (19505.1), showing no significant homology to any known gene

SEQ ID NO: 227 is the determined cDNA sequence of 19486.1, showing homology to type I epidermal keratin

SEQ ID NO: 228 is the determined cDNA sequence of 19510.1, showing homology to glucose transporter for glycoprotein

SEQ ID NO: 229 is the determined cDNA sequence of 19512.1, showing homology to the human lysyl hydroxylase gene

SEQ ID NO: 230 is the determined cDNA sequence of 19511.1, showing homology to human palimotoyl-protein thioesterase

SEQ ID NO: 231 is the determined cDNA sequence of 19508.1, showing homology to human alpha enolase

SEQ ID NO: 232 is the determined cDNA sequence of B807P (19509.1), showing no significant homology to any known gene

SEQ ID NO: 233 is the determined cDNA sequence of B809P (19520.1), showing homology to clone 102D24 on chromosome 11q13.31

SEQ ID NO: 234 is the determined cDNA sequence of 19507.1, showing homology toprosome beta-subunit

SEQ ID NO: 235 is the determined cDNA sequence of 19525.1, showing homology to human pro-urokinase precursor

SEQ ID NO: 236 is the determined cDNA sequence of 19513.1, showing no significant homology to any known gene

SEQ ID NO: 237 is the determined cDNA sequence of 19517.1, showing homology to human PAC 128M19 clone

SEQ ID NO: 238 is the determined cDNA sequence of 19564.1, showing homology to human cytochrome P450-IIB

SEQ ID NO: 239 is the determined cDNA sequence of 19553.1, showing homology to human GABA-A receptor pi subunit

SEQ ID NO: 240 is the determined cDNA sequence of B811P (19575.1), showing no significant homology to any known gene

SEQ ID NO: 241 is the determined cDNA sequence of B810P (19560.1), showing no significant homology to any known gene

SEQ ID NO: 242 is the determined cDNA sequence of 19588.1, showing homology to aortic carboxypetidase-like protein

SEQ ID NO: 243 is the determined cDNA sequence of 19551.1, showing homology to human BCL-1 gene

SEQ ID NO: 244 is the determined cDNA sequence of 19567.1, showing homology to human proteasome-related mRNA

SEQ ID NO: 245 is the determined cDNA sequence of B803P (19583.1), showing no significant homology to any known gene

SEQ ID NO: 246 is the determined cDNA sequence of B812P (19587.1), showing no significant homology to any known gene

SEQ ID NO: 247 is the determined cDNA sequence of B802P (19392.2), showing homology to human chromosome 17

SEQ ID NO: 248 is the determined cDNA sequence of 19393.2, showing homology to human nicein B2 chain

SEQ ID NO: 249 is the determined cDNA sequence of 19398.2, human MHC class II DQ alpha mRNA

SEQ ID NO: 250 is the determined cDNA sequence of B804P (19399.2), showing homology to human Xp22 BAC GSHB-184P14

SEQ ID NO: 251 is the determined cDNA sequence of 19401.2, showing homology to human ikB kinase-b gene

SEQ ID NO: 252 is the determined cDNA sequence of 20266, showing no significant homology to any known gene

SEQ ID NO: 253 is the determined cDNA sequence of B826P (20270), showing no significant homology to any known gene

SEQ ID NO: 254 is the determined cDNA sequence of 20274, showing no significant homology to any known gene

SEQ ID NO: 255 is the determined cDNA sequence of 20276, showing no significant homology to any known gene

SEQ ID NO: 256 is the determined cDNA sequence of 20277, showing no significant homology to any known gene

SEQ ID NO: 257 is the determined cDNA sequence of B823P (20280), showing no significant homology to any known gene

SEQ ID NO: 258 is the determined cDNA sequence of B821P (20281), showing no significant homology to any known gene

SEQ ID NO: 259 is the determined cDNA sequence of B824P (20294), showing no significant homology to any known gene

SEQ ID NO: 260 is the determined cDNA sequence of 20303, showing no significant homology to any known gene

SEQ ID NO: 261 is the determined cDNA sequence of B820P (20310), showing no significant homology to any known gene

SEQ ID NO: 262 is the determined cDNA sequence of B825P (20336), showing no significant homology to any known gene

SEQ ID NO: 263 is the determined cDNA sequence of B827P (20341), showing no significant homology to any known gene

SEQ ID NO: 264 is the determined cDNA sequence of 20941, showing no significant homology to any known gene

SEQ ID NO: 265 is the determined cDNA sequence of 20954, showing no significant homology to any known gene

SEQ ID NO: 266 is the determined cDNA sequence of 20961, showing no significant homology to any known gene

SEQ ID NO: 267 is the determined cDNA sequence of 20965, showing no significant homology to any known gene

SEQ ID NO: 268 is the determined cDNA sequence of 20975, showing no significant homology to any known gene

SEQ ID NO: 269 is the determined cDNA sequence of 20261, showing homology to Human p120 catenin

SEQ ID NO: 270 is the determined cDNA sequence of B822P (20262), showing homology to Human membrane glycoprotein 4F2

SEQ ID NO: 271 is the determined cDNA sequence of 20265, showing homology to Human Na, K-ATPase Alpha 1

SEQ ID NO: 272 is the determined cDNA sequence of 20267, showing homology to Human heart HS 90, partial cds

SEQ ID NO: 273 is the determined cDNA sequence of 20268, showing homology to Human mRNA GPI-anchored protein p137

SEQ ID NO: 274 is the determined cDNA sequence of 20271, showing homology to Human cleavage stimulation factor 77 kDa subunit

SEQ ID NO: 275 is the determined cDNA sequence of 20272, showing homology to Human p190-B

SEQ ID NO: 276 is the determined cDNA sequence of 20273, showing homology to Human ribophorin

SEQ ID NO: 277 is the determined cDNA sequence of 20278, showing homology to Human ornithine amino transferase

SEQ ID NO: 278 is the determined cDNA sequence of 20279, showing homology to Human S-adenosylmethionine synthetase

SEQ ID NO: 279 is the determined cDNA sequence of 20293, showing homology to Human x inactivation transcript

SEQ ID NO: 280 is the determined cDNA sequence of 20300, showing homology to Human cytochrome p450

SEQ ID NO: 281 is the determined cDNA sequence of 20305, showing homology to Human elongation factor-1 alpha

SEQ ID NO: 282 is the determined cDNA sequence of 20306, showing homology to Human epithelial ets protein

SEQ ID NO: 283 is the determined cDNA sequence of 20307, showing homology to Human signal transducer mRNA

SEQ ID NO: 284 is the determined cDNA sequence of 20313, showing homology to Human GABA-A receptor pi subunit mRNA

SEQ ID NO: 285 is the determined cDNA sequence of 20317, showing homology to Human tyrosine phosphatase

SEQ ID NO: 286 is the determined cDNA sequence of 20318, showing homology to Human cathepsine B proteinase

SEQ ID NO: 287 is the determined cDNA sequence of 20320, showing homology to Human 2-phosphopyruvate-hydratase-alpha-enolase

SEQ ID NO: 288 is the determined cDNA sequence of 20321, showing homology to Human E-cadherin

SEQ ID NO: 289 is the determined cDNA sequence of 20322, showing homology to Human hsp86

SEQ ID NO: 290 is the determined cDNA sequence of B828P (20326), showing homology to Human x inactivation transcript

SEQ ID NO: 291 is the determined cDNA sequence of 20333, showing homology to Human chromatin regulator, SMARCA5

SEQ ID NO: 292 is the determined cDNA sequence of 20335, showing homology to Human sphingolipid activator protein 1

SEQ ID NO: 293 is the determined cDNA sequence of 20337, showing homology to Human hepatocyte growth factor activator inhibitor type 2

SEQ ID NO: 294 is the determined cDNA sequence of 20338, showing homology to Human cell adhesion molecule CD44

SEQ ID NO: 295 is the determined cDNA sequence of 20340, showing homology to Human nuclear factor (erythroid-derived)-like 1

SEQ ID NO: 296 is the determined cDNA sequence of 20938, showing homology to Human vinculin mRNA

SEQ ID NO: 297 is the determined cDNA sequence of 20939, showing homology to Human elongation factor EF-1-alpha

SEQ ID NO: 298 is the determined cDNA sequence of 20940, showing homology to Human nestin gene

SEQ ID NO: 299 is the determined cDNA sequence of 20942, showing homology to Human pancreatic ribonuclease

SEQ ID NO: 300 is the determined cDNA sequence of 20943, showing homology to Human transcobalamin I

SEQ ID NO: 301 is the determined cDNA sequence of 20944, showing homology to Human beta-tubulin

SEQ ID NO: 302 is the determined cDNA sequence of 20946, showing homology to Human HS1 protein

SEQ ID NO: 303 is the determined cDNA sequence of 20947, showing homology to Human cathepsin B

SEQ ID NO: 304 is the determined cDNA sequence of 20948, showing homology to Human testis enhanced gene transcript

SEQ ID NO: 305 is the determined cDNA sequence of 20949, showing homology to Human elongation factor EF-1-alpha

SEQ ID NO: 306 is the determined cDNA sequence of 20950, showing homology to Human ADP-ribosylation factor 3

SEQ ID NO: 307 is the determined cDNA sequence of 20951, showing homology to Human IFP53 or WRS for tryptophanyl-tRNA synthetase

SEQ ID NO: 308 is the determined cDNA sequence of 20952, showing homology to Human cyclin-dependent protein kinase

SEQ ID NO: 309 is the determined cDNA sequence of 20957, showing homology to Human alpha-tubulin isoform 1

SEQ ID NO: 310 is the determined cDNA sequence of 20959, showing homology to Human tyrosine phosphatase-61bp deletion

SEQ ID NO: 311 is the determined cDNA sequence of 20966, showing homology to Human tyrosine phosphatase

SEQ ID NO: 312 is the determined cDNA sequence of B830P (20976), showing homology to Human nuclear factor NF 45

SEQ ID NO: 313 is the determined cDNA sequence of B829P (20977), showing homology to Human delta-6 fatty acid desaturase

SEQ ID NO: 314 is the determined cDNA sequence of 20978, showing homology to Human nuclear aconitase

SEQ ID NO: 315 is the determined cDNA sequence of clone 23176.

SEQ ID NO: 316 is the determined cDNA sequence of clone 23140.

SEQ ID NO: 317 is the determined cDNA sequence of clone 23166.

SEQ ID NO: 318 is the determined cDNA sequence of clone 23167.

SEQ ID NO: 319 is the determined cDNA sequence of clone 23177.

SEQ ID NO: 320 is the determined cDNA sequence of clone 23217.

SEQ ID NO: 321 is the determined cDNA sequence of clone 23169.

SEQ ID NO: 322 is the determined cDNA sequence of clone 23160.

SEQ ID NO: 323 is the determined cDNA sequence of clone 23182.

SEQ ID NO: 324 is the determined cDNA sequence of clone 23232.

SEQ ID NO: 325 is the determined cDNA sequence of clone 23203.

SEQ ID NO: 326 is the determined cDNA sequence of clone 23198.

SEQ ID NO: 327 is the determined cDNA sequence of clone 23224.

SEQ ID NO: 328 is the determined cDNA sequence of clone 23142.

SEQ ID NO: 329 is the determined cDNA sequence of clone 23138.

SEQ ID NO: 330 is the determined cDNA sequence of clone 23147.

SEQ ID NO: 331 is the determined cDNA sequence of clone 23148.

SEQ ID NO: 332 is the determined cDNA sequence of clone 23149.

SEQ ID NO: 333 is the determined cDNA sequence of clone 23172.

SEQ ID NO: 334 is the determined cDNA sequence of clone 23158.

SEQ ID NO: 335 is the determined cDNA sequence of clone 23156.

SEQ ID NO: 336 is the determined cDNA sequence of clone 23221.

SEQ ID NO: 337 is the determined cDNA sequence of clone 23223.

SEQ ID NO: 338 is the determined cDNA sequence of clone 23155.

SEQ ID NO: 339 is the determined cDNA sequence of clone 23225.

SEQ ID NO: 340 is the determined cDNA sequence of clone 23226.

SEQ ID NO: 341 is the determined cDNA sequence of clone 23228.

SEQ ID NO: 342 is the determined cDNA sequence of clone 23229.
SEQ ID NO: 343 is the determined cDNA sequence of clone 23231.
SEQ ID NO: 344 is the determined cDNA sequence of clone 23154.
SEQ ID NO: 345 is the determined cDNA sequence of clone 23157.
SEQ ID NO: 346 is the determined cDNA sequence of clone 23153.
SEQ ID NO: 347 is the determined cDNA sequence of clone 23159.
SEQ ID NO: 348 is the determined cDNA sequence of clone 23152.
SEQ ID NO: 349 is the determined cDNA sequence of clone 23161.
SEQ ID NO: 350 is the determined cDNA sequence of clone 23162.
SEQ ID NO: 351 is the determined cDNA sequence of clone 23163.
SEQ ID NO: 352 is the determined cDNA sequence of clone 23164.
SEQ ID NO: 353 is the determined cDNA sequence of clone 23165.
SEQ ID NO: 354 is the determined cDNA sequence of clone 23151.
SEQ ID NO: 355 is the determined cDNA sequence of clone 23150.
SEQ ID NO: 356 is the determined cDNA sequence of clone 23168.
SEQ ID NO: 357 is the determined cDNA sequence of clone 23146.
SEQ ID NO: 358 is the determined cDNA sequence of clone 23170.
SEQ ID NO: 359 is the determined cDNA sequence of clone 23171.
SEQ ID NO: 360 is the determined cDNA sequence of clone 23145.
SEQ ID NO: 361 is the determined cDNA sequence of clone 23174.
SEQ ID NO: 362 is the determined cDNA sequence of clone 23175.
SEQ ID NO: 363 is the determined cDNA sequence of clone 23144.
SEQ ID NO: 364 is the determined cDNA sequence of clone 23178.
SEQ ID NO: 365 is the determined cDNA sequence of clone 23179.
SEQ ID NO: 366 is the determined cDNA sequence of clone 23180.
SEQ ID NO: 367 is the determined cDNA sequence of clone 23181.
SEQ ID NO: 368 is the determined cDNA sequence of clone 23143
SEQ ID NO: 369 is the determined cDNA sequence of clone 23183.
SEQ ID NO: 370 is the determined cDNA sequence of clone 23184.
SEQ ID NO: 371 is the determined cDNA sequence of clone 23185.
SEQ ID NO: 372 is the determined cDNA sequence of clone 23186.
SEQ ID NO: 373 is the determined cDNA sequence of clone 23187.
SEQ ID NO: 374 is the determined cDNA sequence of clone 23190.

SEQ ID NO: 375 is the determined cDNA sequence of clone 23189.
SEQ ID NO: 376 is the determined cDNA sequence of clone 23202.
SEQ ID NO: 378 is the determined cDNA sequence of clone 23191.
SEQ ID NO: 379 is the determined cDNA sequence of clone 23188.
SEQ ID NO: 380 is the determined cDNA sequence of clone 23194.
SEQ ID NO: 381 is the determined cDNA sequence of clone 23196.
SEQ ID NO: 382 is the determined cDNA sequence of clone 23195.
SEQ ID NO: 383 is the determined cDNA sequence of clone 23193.
SEQ ID NO: 384 is the determined cDNA sequence of clone 23199.
SEQ ID NO: 385 is the determined cDNA sequence of clone 23200.
SEQ ID NO: 386 is the determined cDNA sequence of clone 23192.
SEQ ID NO: 387 is the determined cDNA sequence of clone 23201.
SEQ ID NO: 388 is the determined cDNA sequence of clone 23141.
SEQ ID NO: 389 is the determined cDNA sequence of clone 23139.
SEQ ID NO: 390 is the determined cDNA sequence of clone 23204.
SEQ ID NO: 391 is the determined cDNA sequence of clone 23205.
SEQ ID NO: 392 is the determined cDNA sequence of clone 23206.
SEQ ID NO: 393 is the determined cDNA sequence of clone 23207.
SEQ ID NO: 394 is the determined cDNA sequence of clone 23208.
SEQ ID NO: 395 is the determined cDNA sequence of clone 23209.
SEQ ID NO: 396 is the determined cDNA sequence of clone 23210.
SEQ ID NO: 397 is the determined cDNA sequence of clone 23211.
SEQ ID NO: 398 is the determined cDNA sequence of clone 23212.
SEQ ID NO: 399 is the determined cDNA sequence of clone 23214.
SEQ ID NO: 400 is the determined cDNA sequence of clone 23215.
SEQ ID NO: 401 is the determined cDNA sequence of clone 23216.
SEQ ID NO: 402 is the determined cDNA sequence of clone 23137.
SEQ ID NO: 403 is the determined cDNA sequence of clone 23218.
SEQ ID NO: 404 is the determined cDNA sequence of clone 23220.
SEQ ID NO: 405 is the determined cDNA sequence of clone 19462.
SEQ ID NO: 406 is the determined cDNA sequence of clone 19430.
SEQ ID NO: 407 is the determined cDNA sequence of clone 19407.
SEQ ID NO: 408 is the determined cDNA sequence of clone 19448.

SEQ ID NO: 409 is the determined cDNA sequence of clone 19447.

SEQ ID NO: 410 is the determined cDNA sequence of clone 19426.

SEQ ID NO: 411 is the determined cDNA sequence of clone 19441.

SEQ ID NO: 412 is the determined cDNA sequence of clone 19454.

SEQ ID NO: 413 is the determined cDNA sequence of clone 19463.

SEQ ID NO: 414 is the determined cDNA sequence of clone 19419.

SEQ ID NO: 415 is the determined cDNA sequence of clone 19434.

SEQ ID NO: 416 is the determined extended cDNA sequence of B820P.

SEQ ID NO: 417 is the determined extended cDNA sequence of B821P.

SEQ ID NO: 418 is the determined extended cDNA sequence of B822P.

SEQ ID NO: 419 is the determined extended cDNA sequence of B823P.

SEQ ID NO: 420 is the determined extended cDNA sequence of B824P.

SEQ ID NO: 421 is the determined extended cDNA sequence of B825P.

SEQ ID NO: 422 is the determined extended cDNA sequence of B826P.

SEQ ID NO: 423 is the determined extended cDNA sequence of B827P.

SEQ ID NO: 424 is the determined extended cDNA sequence of B828P.

SEQ ID NO: 425 is the determined extended cDNA sequence of B829P.

SEQ ID NO: 426 is the determined extended cDNA sequence of B830P.

SEQ ID NO: 427 is the determined cDNA sequence of clone 266B4.

SEQ ID NO: 428 is the determined cDNA sequence of clone 22892.

SEQ ID NO: 429 is the determined cDNA sequence of clone 266G3.

SEQ ID NO: 430 is the determined cDNA sequence of clone 22890.

SEQ ID NO: 431 is the determined cDNA sequence of clone 264B4.

SEQ ID NO: 432 is the determined cDNA sequence of clone 22883.

SEQ ID NO: 433 is the determined cDNA sequence of clone 22882.

SEQ ID NO: 434 is the determined cDNA sequence of clone 22880.

SEQ ID NO: 435 is the determined cDNA sequence of clone 263G1.

SEQ ID NO: 436 is the determined cDNA sequence of clone 263G6.

SEQ ID NO: 437 is the determined cDNA sequence of clone 262B2.

SEQ ID NO: 438 is the determined cDNA sequence of clone 262B6.

SEQ ID NO: 439 is the determined cDNA sequence of clone 22869.

SEQ ID NO: 440 is the determined cDNA sequence of clone 21374.

SEQ ID NO: 441 is the determined cDNA sequence of clone 21362.

SEQ ID NO: 442 is the determined cDNA sequence of clone 21349.

SEQ ID NO: 443 is the determined cDNA sequence of clone 21309.

SEQ ID NO: 444 is the determined cDNA sequence of clone 21097.

SEQ ID NO: 445 is the determined cDNA sequence of clone 21096.

SEQ ID NO: 446 is the determined cDNA sequence of clone 21094.

SEQ ID NO: 447 is the determined cDNA sequence of clone 21093.

SEQ ID NO: 448 is the determined cDNA sequence of clone 21091.

SEQ ID NO: 449 is the determined cDNA sequence of clone 21089.

SEQ ID NO: 450 is the determined cDNA sequence of clone 21087.

SEQ ID NO: 451 is the determined cDNA sequence of clone 21085.

SEQ ID NO: 452 is the determined cDNA sequence of clone 21084.

SEQ ID NO: 453 is a first partial cDNA sequence of clone 2BT1-40.

SEQ ID NO: 454 is a second partial cDNA sequence of clone 2BT1-40.

SEQ ID NO: 455 is the determined cDNA sequence of clone 21063.

SEQ ID NO: 456 is the determined cDNA sequence of clone 21062.

SEQ ID NO: 457 is the determined cDNA sequence of clone 21060.

SEQ ID NO: 458 is the determined cDNA sequence of clone 21053.

SEQ ID NO: 459 is the determined cDNA sequence of clone 21050.

SEQ ID NO: 460 is the determined cDNA sequence of clone 21036.

SEQ ID NO: 461 is the determined cDNA sequence of clone 21037.

SEQ ID NO: 462 is the determined cDNA sequence of clone 21048.

SEQ ID NO: 463 is a consensus DNA sequence of B726P (referred to as B726P-spliced_seq_B726P).

SEQ ID NO: 464 is the determined cDNA sequence of a second splice form of B726P (referred to as 27490.seq_B726P).

SEQ ID NO: 465 is the determined cDNA sequence of a third splice form of B726P (referred to as 27068.seq_B726P).

SEQ ID NO: 466 is the determined cDNA sequence of a second splice form of B726P (referred to as 23113.seq_B726P).

SEQ ID NO: 467 is the determined cDNA sequence of a second splice form of B726P (referred to as 23103.seq_B726P).

SEQ ID NO: 468 is the determined cDNA sequence of a second splice form of B726P (referred to as 19310.seq_B726P).

SEQ ID NO: 469 is the predicted amino acid sequence encoded by the upstream ORF of SEQ ID NO: 463.

SEQ ID NO: 470 is the predicted amino acid sequence encoded by SEQ ID NO: 464.

SEQ ID NO: 471 is the predicted amino acid sequence encoded by SEQ ID NO: 465.

SEQ ID NO: 472 is the predicted amino acid sequence encoded by SEQ ID NO: 466.

SEQ ID NO: 473 is the predicted amino acid sequence encoded by SEQ ID NO: 467.

SEQ ID NO: 474 is the determined cDNA sequence for an alternative splice form of B726P.

SEQ ID NO: 475 is the amino acid sequence encoded by SEQ ID NO: 474.

SEQ ID NO: 476 is the isolated cDNA sequence of B720P.

SEQ ID NO: 477 is the cDNA sequence of a known keratin gene.

SEQ ID NO: 478 is the amino acid sequence encoded by SEQ ID NO: 477.

SEQ ID NO: 479 is the determined cDNA sequence for clone 19465.

SEQ ID NO: 480 and 481 are PCR primers.

SEQ ID NO: 482 is the cDNA sequence for the expressed downstream ORF of B726P.

SEQ ID NO: 483 is the amino acid sequence for the expressed recombinant downstream ORF of B726P.

SEQ ID NO: 484 is the determined full-length cDNA sequence for B720P.

SEQ ID NO: 485 is the amino acid sequence encoded by SEQ ID NO: 484.

SEQ ID NO: 486 is the determined cDNA sequence of a truncated form of B720P, referred to as B720P-tr.

SEQ ID NO: 487 is the amino acid sequence of B720P-tr.

SEQ ID NO: 488 is the amino acid sequence of a naturally processed epitope of B726P recognized by B726P-specific CTL.

SEQ ID NO: 489 is a DNA sequence encoding the B726P epitope set forth in SEQ ID NO: 488.

SEQ ID NO: 490 is a DNA sequence encoding a fusion protein wherein mammaglobin is fused to a B726P combined upstream and downstream open reading frame (ORF) (the amino acid sequence of the B726P combined ORF is disclosed herein by SEQ ID NO: 475 which is encoded by the DNA sequence of SEQ ID NO: 474).

SEQ ID NO: 491 is a DNA sequence encoding a fusion protein wherein mammaglobin is fused to a B726P upstream ORF (the amino acid sequence of the B726P upstream ORF is disclosed herein by SEQ ID NO: 469 which is encoded by the DNA sequence of SEQ ID NO: 463).

SEQ ID NO: 492 is a DNA sequence encoding a fusion protein wherein mammaglobin is fused to a B726P downstream ORF (the amino acid sequence of the B726P downstream ORF is disclosed herein by SEQ ID NO: 176 which is encoded by the DNA sequence of SEQ ID NO: 175).

SEQ ID NO: 493 is the amino acid sequence encoded by the DNA sequence of SEQ ID NO: 490.

SEQ ID NO: 494 is the amino acid sequence encoded by the DNA sequence of SEQ ID NO: 491.

SEQ ID NO: 495 is the amino acid sequence encoded by the DNA sequence of SEQ ID NO: 492.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as breast cancer. Certain illustrative compositions described herein include breast tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.,* T cells). A "breast tumor protein," as the term is used herein, refers generally to a protein that is expressed in breast tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain breast tumor

proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with breast cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487 and 488, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human breast cancer.

POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.,* an endogenous sequence that encodes a breast tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.

In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or

more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at

least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear

minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also

in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto,

CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as breast tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a breast tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques,

amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia *et al.*, *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom *et al.*, *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker *et al.*, *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding

sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.)

may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J. 3*:1671-1680; Broglie, R. *et al.* (1984) *Science 224*:838-843; and Winter, J. *et al.* (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda

cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. *et al.* (1994) *Proc. Natl. Acad. Sci. 91* :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and

characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. *et al.* (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. *et al.* (1980) *Proc. Natl. Acad. Sci. 77*:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol. 150*:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci. 85*:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol. 55*:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA

probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif. 3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol. 12*:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using

solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc. 85*:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule

relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated

herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCR™, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α-thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the

products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (*e.g.*, biotin) and/or a detector moiety (*e.g.*, enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.*, 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by

reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are:

isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (–0.4); threonine (–0.7); serine (–0.8); tryptophan (–0.9); tyrosine (–1.3); proline (–1.6); histidine (–3.2); glutamate (–3.5); glutamine (–3.5); aspartate (–3.5); asparagine (–3.5); lysine (–3.9); and arginine (–4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (–0.4); proline (–0.5 ± 1); alanine (–0.5); histidine (–0.5); cysteine (–1.0); methionine (–1.3); valine (–1.5); leucine (–1.8); isoleucine (–1.8); tyrosine (–2.3); phenylalanine (–2.5); tryptophan (–3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety or well known approaches, several of which are outlined below for the purpose of illustration.

1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement

has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5′-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package

approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may

be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*, 10^9-10^{11} plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993),

peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5′ and 3′ ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins,

and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B

virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected

polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic

antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal $GABA_A$ receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m, binding

energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-*ras*, c-*fos* and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target

RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of

these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*, 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described

in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5′-end, and phosphoramidites at the 3′-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2′-amino, 2′-C-allyl, 2′-flouro, 2′-o-methyl, 2′-H (for a review see *e.g.,* Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions

of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993; L'Huillier *et al.*, 1992; Lisziewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational

therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs

recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3′ to 5′ polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends

telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.*, 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification (Orum *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487 and 488, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO: 176, 179, 181, 469-473, 475, 485, 487 and 488.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a breast tumor protein or a variant thereof, as described herein. As noted above, a " breast tumor protein" is a protein that is expressed by breast tumor cells. Proteins that are breast tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with breast cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.,* specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a breast tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.,* 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.,* they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native breast tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.,* in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such

screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As noted above, a composition may comprise a variant of a native breast tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native breast tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.,* 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively

charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange

resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* *85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase.

This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene 40*:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute *et al. New Engl. J. Med.*, *336*:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at

least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

In order to improve the antigenicity and/or immunogenicity of breast tumor proteins according to the present invention, fusion proteins comprising antigenic and/or immunogenic portions of two or more breast tumor proteins may be prepared. Exemplary breast tumor fusion proteins may be prepared through conventional recombinant DNA methodology by combining a DNA sequence encoding mammaglobin with a DNA sequence encoding either (1) the combined B726P upstream and downstream ORFs (SEQ ID NO: 490), (2) the upstream B726P ORF (SEQ ID NO: 491), and/or (3) the downstream B726P ORF (SEQ ID NO: 492). *See, e.g.*, Ausubel, F.M. *et al.*, "Short Protocols in Molecular Biology" (4nd ed. 1999); incorporated herein by reference in its entirety). Exemplary fusion proteins are disclosed herein by SEQ ID NO: 493 (mammaglobin-combined B726P ORF), SEQ ID NO: 494 (mammaglobin-upstream B726P ORF), and SEQ ID NO: 495 (mammaglobin-downstream B726P ORF). The DNA sequence encoding mammaglobin is disclosed herein by nucleotides 1-279 of SEQ ID NOs: 490-492 and the corresponding mammaglobin amino acid sequence is disclosed herein as amino acids 1-93 of SEQ ID NOs: 493-495. *See, also,* U.S. Patent No. 5,668,267; U.S. Patent No. 5,922,836; U.S. Patent No. 5,855,889; U.S. Patent No. 5,968,754; and U.S. Patent No. 6,004,756, each of which U.S. Patent is incorporated by reference herein in its entirety.

In addition to the exemplary fusion proteins prepared by the fusion of a full-length mammaglobin coding region with various B726P coding regions, the present invention further provides fusion proteins comprising immunogenic portions of 9 or more contiguous amino acids from either or both of mammaglobin and B726P. More preferably, immunogenic portions may be 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more contiguous amino acids from either or both of mammaglobin and/or B726P. Alternatively, immunogenic portions may be at least 25, 30, 35, 40, 45, 50, 75, 100, 250, 500, or 1095 contiguous amino acids from either or both of mammaglobin and/or

B726P and may also include any integral number of amino acids between 20 and 1095 contiguous amino acids from either or both of mammaglobin and/or B726P.

Representative immunogenic portions of mammaglobin are disclosed in co-pending U.S. Patent Application 60/136,528. Exemplary immunogenic portions include the following mammaglobin peptide sequences: IDELKECFLNQTDETLSNVE (amino acids 59-78 of SEQ ID NO: 493); TTNAIDELKECFLNQ (amino acids 55-69 of SEQ ID NO: 493); SQHCYAGSGCPLLENVISKTI (amino acids 13-33 of SEQ ID NO: 493); EYKELLQEFIDDNATTNAID (amino acids 41-60 of SEQ ID NO: 493), and/or KLLMVLMLA (amino acids 2-10 of SEQ ID NO: 493). Other preferred epitopes comprise a glycosylation site of mammaglobin. Such epitopes are particularly useful for the generation of antibodies that specifically bind to glycosylated mammaglobin. Two such sites are the N-linked glycosylation sites asparagine (Asp)-53 (QEFIDDNATTNAI; amino acids 47-59 of SEQ ID NO: 493) and Asp-68 (LKECFLNQTDETL; amino acids 62-74 of SEQ ID NO: 493).

The present invention also contemplates that a wide variety of immunogenic portions from the B726P combined, B726P upstream, and/or B726P downstream amino acid sequences may find use in mammaglobin-B726P fusion proteins. For example, a particularly suitable mammaglobin-B726P fusion protein may be prepared by fusing mammaglobin to a downstream B726P epitope recognized by B726P-specific CTL clones, described herein in Example 4, which epitope is included within the N-terminal end of the downstream region of B726P (*i.e.* amino acids 1-129 of SEQ ID NO: 176).

It will be apparent to those of skill in the art that the precise amino acid sequence and primary sequence arrangement of the mammaglobin and/or B726P portions of the fusion proteins may be varied without deviating from the scope of the present invention. For example, conservative amino acids substitutions within either or both of the mammaglobin or B726P portions may be made, for example, to achieve fusion proteins having improved properties such as increased protein stability and/or immunogenicity. In addition, the present invention contemplates that the mammaglobin

portion may be fused to either the N-terminus or C-terminus of the B726P portion to achieve fusion proteins that have the desired antigenic and/or immunogenic properties.

Fusion proteins according to the present invention, as exemplified by the mammaglobin-B726P fusion proteins disclosed herein by this Example, will find use as cancer vaccines, reagents for antibody therapeutics, and/or in various diagnostic assays. It is expected that these fusion proteins will have improved antigenic and/or immunogenic properties as compared to either the mammaglobin and/or B726P proteins alone.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a breast tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a breast tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a breast tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as breast cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a breast tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a

cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol. 6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may

be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers

include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter *et al.*), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn *et al.*), by

serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler *et al.*).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato *et al.*), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih *et al.*). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a breast tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a breast tumor polypeptide, polynucleotide encoding a breast tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a breast tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a breast tumor polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res. 54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a breast tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above

for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan *et al.*, Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a breast tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Breast tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a breast tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a breast tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a breast tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a breast tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues.

The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup of elixir

may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even

intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will

be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the

introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran *et al.*, 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μm. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are

sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be are easily made, as described (Couvreur *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

IMMUNOGENIC COMPOSITIONS

In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable

microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch *et al.*, *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner *et al.*, *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner *et al.*, *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld *et al.*, *Science 252*:431-434, 1991; Kolls *et al.*, *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler *et al.*, *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman *et al.*, *Circulation 88*:2838-2848, 1993; and Guzman *et al.*, *Cir. Res. 73*:1202-1207, 1993.

Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer *et al.*, *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will

increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science 273*:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be

administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes *et al.*, *Vaccine 14*:1429-1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (*see* Zitvogel *et al.*, *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high

expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a breast tumor protein (or portion or other variant thereof) such that the breast tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi *et al.*, *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the breast tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as breast cancer. Within such

methods, pharmaceutical compositions and immunogenic compositions are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever *et al.*, *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and immunogenic compositions may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be

appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a breast tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more breast tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as breast cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the

biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a breast tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length breast tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S.

Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate

(generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett *et al.*, *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a

region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use breast tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such breast tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a breast tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a breast tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample

in the absence of breast tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a breast tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a breast tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the breast tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a breast tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a breast tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477 479, 484, 486 and 489. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple breast tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that

results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a breast tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a breast tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a breast tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a breast tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES

This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

A cDNA subtraction library containing cDNA from breast tumor subtracted with normal breast cDNA was constructed as follows. Total RNA was extracted from primary tissues using Trizol reagent (Gibco BRL Life Technologies, Gaithersburg, MD) as described by the manufacturer. The polyA+ RNA was purified using an oligo(dT) cellulose column according to standard protocols. First strand cDNA was synthesized using the primer supplied in a Clontech PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, CA). The driver DNA consisted of cDNAs from two normal breast tissues with the tester cDNA being from three primary breast tumors. Double-stranded cDNA was synthesized for both tester and driver, and digested with a combination of endonucleases (MluI, MscI, PvuII, SalI and StuI) which recognize six base pairs DNA. This modification increased the average cDNA size dramatically compared with cDNAs generated according to the protocol of Clontech (Palo Alto, CA). The digested tester cDNAs were ligated to two different adaptors and the subtraction was performed according to Clontech's protocol. The subtracted cDNAs were subjected to two rounds of PCR amplification, following the manufacturer's protocol. The resulting PCR products were subcloned into the TA cloning vector, pCRII (Invitrogen, San Diego, CA) and transformed into ElectroMax *E. coli* DH10B cells (Gibco BRL Life, Technologies) by electroporation. DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division (Foster City, CA) Automated Sequencer Model 373A.

Sixty-three distinct cDNA clones were found in the subtracted breast tumor-specific cDNA library. The determined one strand (5' or 3') cDNA sequences for the clones are provided in SEQ ID NO: 1-61, 72 and 73, respectively. Comparison of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences

provided in SEQ ID NO: 14, 21, 22, 27, 29, 30, 32, 38, 44, 45, 53, 72 and 73. The sequences of SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60 and 61 were found to represent known human genes. The sequences of SEQ ID NO: 2, 4, 23, 39 and 50 were found to show some similarity to previously identified non-human genes. The remaining clones (SEQ ID NO: 5-13, 15, 18-20, 24-26, 28, 31, 33, 35-37, 40-43, 46, 47, 49, 51, 52, 54-56, 58 and 59) were found to show at least some degree of homology to previously identified expressed sequence tags (ESTs).

To determine mRNA expression levels of the isolated cDNA clones, cDNA clones from the breast subtraction described above were randomly picked and colony PCR amplified. Their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were arrayed onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. Data was analyzed using Synteni provided GEMTOOLS Software. Of the seventeen cDNA clones examined, those of SEQ ID NO: 40, 46, 59 and 73 were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, PBMC, colon, fetal tissue, salivary gland, bone marrow, lung, pancreas, large intestine, spinal cord, adrenal gland, kidney, pancreas, liver, stomach, skeletal muscle, heart, small intestine, skin, brain and human mammary epithelial cells). The clones of SEQ ID NO: 41 and 48 were found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested, with the exception of bone marrow. The clone of SEQ ID NO: 42 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested except bone marrow and spinal cord. The clone of SEQ ID NO: 43 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord, heart and small intestine. The clone of SEQ ID NO: 51 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large intestine. The clone of SEQ ID NO: 54 was found to be over-expressed in breast tumor and

expressed at low levels in all other tissues tested with the exception of PBMC, stomach and small intestine. The clone of SEQ ID NO: 56 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large and small intestine, human mammary epithelia cells and SCID mouse-passaged breast tumor. The clone of SEQ ID NO: 60 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord and heart. The clone of SEQ ID NO: 61 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of small intestine. The clone of SEQ ID NO: 72 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of colon and salivary gland.

The results of a Northern blot analysis of the clone SYN18C6 (SEQ ID NO: 40) are shown in Fig. 1. A predicted protein sequence encoded by SYN18C6 is provided in SEQ ID NO: 62.

Additional cDNA clones that are over-expressed in breast tumor tissue were isolated from breast cDNA subtraction libraries as follows. Breast subtraction libraries were prepared, as described above, by PCR-based subtraction employing pools of breast tumor cDNA as the tester and pools of either normal breast cDNA or cDNA from other normal tissues as the driver. cDNA clones from breast subtraction were randomly picked and colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using the microarray technology described above. Twenty-four distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, brain, liver, pancreas, lung, salivary gland, stomach, colon, kidney, bone marrow, skeletal muscle, PBMC, heart, small intestine, adrenal gland, spinal cord, large intestine and skin). The determined cDNA sequences for these clones are provided in SEQ ID NO: 63-87. Comparison of the sequences of SEQ ID NO: 74-87 with those in the gene bank as described above, revealed homology to previously identified human genes. No significant homologies were found to the sequences of SEQ ID NO: 63-73.

Three DNA isoforms for the clone B726P (partial sequence provided in SEQ ID NO: 71) were isolated as follows. A radioactive probe was synthesized from

B726P by excising B726P DNA from a pT7Blue vector (Novagen) by a BamHI/XbaI restriction digest and using the resulting DNA as the template in a single-stranded PCR in the presence of [α-32P]dCTP. The sequence of the primer employed for this PCR is provided in SEQ ID NO: 177. The resulting radioactive probe was used to probe a directional cDNA library and a random-primed cDNA library made using RNA isolated from breast tumors. Eighty-five clones were identified, excised, purified and sequenced. Of these 85 clones, three were found to each contain a significant open reading frame. The determined cDNA sequence of the isoform B726P-20 is provided in SEQ ID NO: 175, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 176. The determined cDNA sequence of the isoform B726P-74 is provided in SEQ ID NO: 178, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 179. The determined cDNA sequence of the isoform B726P-79 is provided in SEQ ID NO: 180, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 181.

Efforts to obtain a full-length clone of B726P using standard techniques led to the isolation of five additional clones that represent additional 5' sequence of B726P. These clones appear to be alternative splice forms of the same gene. The determined cDNA sequences of these clones are provided in SEQ ID NO: 464-468, with the predicted amino acid sequences encoded by SEQ ID NO: 464-467 being provided in SEQ ID NO: 470-473, respectively. Using standard computer techniques, a 3,681 bp consensus DNA sequence (SEQ ID NO: 463) was created that contains two large open reading frames. The downstream ORF encodes the amino acid sequence of SEQ ID NO: 181. The predicted amino acid sequence encoded by the upstream ORF is provided in SEQ ID NO: 469. Subsequent studies led to the isolation of an additional splice form of B726P that has 184 bp insert relative to the other forms. This 184 bp insert causes a frameshift that brings the down stream and upstream ORFs together into a single ORF that is 1002 aa in length. The determined cDNA sequence of this alternative splice form is disclosed in SEQ ID NO: 474, with the corresponding amino acid sequence being provided in SEQ ID NO: 475.

Further isolation of individual clones that are over-expressed in breast tumor tissue was conducted using cDNA subtraction library techniques described above. In particular, a cDNA subtraction library containing cDNA from breast tumors

subtracted with five other normal human tissue cDNAs (brain, liver, PBMC, pancreas and normal breast) was utilized in this screening. From the original subtraction, one hundred seventy seven clones were selected to be further characterized by DNA sequencing and microarray analysis. Microarray analysis demonstrated that the sequences in SEQ ID NO: 182-251 and 479 were 2 or more fold over-expressed in human breast tumor tissues over normal human tissues. No significant homologies were found for nineteen of these clones, including, SEQ ID NO: 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246 and 479, with the exception of some previously identified expressed sequence tags (ESTs). The remaining clones share some homology to previously identified genes, specifically SEQ ID NO: 181-184, 187-193, 195-198, 200-204, 206, 207, 209, 210, 212, 213, 217, 218, 220, 221, 223-225, 227-231, 233-235, 237-239, 242-244 and 247-251.

One of the cDNA clones isolated by PCR subtraction as described above (SEQ ID NO: 476; referred to as B720P) which was shown by microarray to be over-expressed in breast tumor tissues, was found to be identical to a known keratin gene. The full-length cDNA sequence of the known keratin gene is provided in SEQ ID NO: 477, with the corresponding amino acid sequence being provided in SEQ ID NO: 478. Primers were generated based on the sequence of SEQ ID NO: 477 and used to clone full-length cDNA from mRNA which was obtained from total RNA showing high expression of B720P in real-time PCR analysis. Products were then cloned and sequenced. The determined full-length cDNA sequence for B720P is provided in SEQ ID NO: 484, with the corresponding amino acid sequence being provided in SEQ ID NO: 485.

In further studies, a truncated form of B720P (referred to as B720P-tr) was identified in breast carcinomas. This antigen was cloned from mRNA derived from total breast tumor RNA that showed high expression of B720P-tr in real-time PCR analysis. mRNA was used to generate a pool of cDNA which was then used as a template to amplify the cDNA corresponding to B720P-tr by PCR. The determined cDNA sequence for B720P-tr is provided in SEQ ID NO: 486. B720P-tr has an ORF of 708 base pairs which encodes a 236 amino acid protein (SEQ ID NO: 487). The size of the transcript was confirmed by northern analysis.

Of the seventy clones showing over-expression in breast tumor tissues, fifteen demonstrated particularly good expression levels in breast tumor over normal

human tissues. The following eleven clones did not show any significant homology to any known genes. Clone 19463.1 (SEQ ID NO: 185) was over-expressed in the majority of breast tumors and also in the SCID breast tumors tested (refer to Example 2); additionally, over-expression was found in a majority of normal breast tissues. Clone 19483.1 (SEQ ID NO: 216) was over-expressed in a few breast tumors, with no over-expression in any normal tissues tested. Clone 19470.1 (SEQ ID NO: 219) was found to be slightly over-expressed in some breast tumors. Clone 19468.1 (SEQ ID NO: 222) was found to be slightly over-expressed in the majority of breast tumors tested. Clone 19505.1 (SEQ ID NO: 226) was found to be slightly over-expressed in 50% of breast tumors, as well as in SCID tumor tissues, with some degree of over-expression in found in normal breast. Clone 1509.1 (SEQ ID NO: 232) was found to be over-expressed in very few breast tumors, but with a certain degree of over-expression in metastatic breast tumor tissues, as well as no significant over-expression found in normal tissues. Clone 19513.1 (SEQ ID NO: 236) was shown to be slightly over-expressed in few breast tumors, with no significant over-expression levels found in normal tissues. Clone 19575.1 (SEQ ID NO: 240) showed low level over-expression in some breast tumors and also in normal breast. Clone 19560.1 (SEQ ID NO: 241) was over-expressed in 50% of breast tumors tested, as well as in some normal breast tissues. Clone 19583.1 (SEQ ID NO: 245) was slightly over-expressed in some breast tumors, with very low levels of over-expression found in normal tissues. Clone 19587.1 (SEQ ID NO: 246) showed low level over-expression in some breast tumors and no significant over-expression in normal tissues.

Clone 19520.1 (SEQ ID NO: 233), showing homology to clone 102D24 on chromosome 11q13.31, was found to be over-expressed in breast tumors and in SCID tumors. Clone 19517.1 (SEQ ID NO: 237), showing homology to human PAC 128M19 clone, was found to be slightly over-expressed in the majority of breast tumors tested. Clone 19392.2 (SEQ ID NO: 247), showing homology to human chromosome 17, was shown to be over-expressed in 50% of breast tumors tested. Clone 19399.2 (SEQ ID NO: 250), showing homology to human Xp22 BAC GSHB-184P14, was shown to be slightly over-expressed in a limited number of breast tumors tested.

In subsequent studies, 64 individual clones were isolated from a subtracted cDNA library containing cDNA from a pool of breast tumors subtracted with

cDNA from five normal tissues (brain, liver, PBMC, pancreas and normal breast). The subtracted cDNA library was prepared as described above with the following modification. A combination of five six-base cutters (MluI, MscI, PvuII, SalI and StuI) was used to digest the cDNA instead of RsaI. This resulted in an increase in the average insert size from 300 bp to 600 bp. The 64 isolated clones were colony PCR amplified and their mRNA expression levels in breast tumor tissue, normal breast and various other normal tissues were examined by microarray technology as described above. The determined cDNA sequences of 11 clones which were found to be over-expressed in breast tumor tissue are provided in SEQ ID NO: 405-415. Comparison of these sequences to those in the public database, as outlined above, revealed homologies between the sequences of SEQ ID NO: 408, 411, 413 and 414 and previously isolated ESTs. The sequences of SEQ ID NO: 405-407, 409, 410, 412 and 415 were found to show some homology to previously identified sequences.

In further studies, a subtracted cDNA library was prepared from cDNA from metastatic breast tumors subtracted with a pool of cDNA from five normal tissues (breast, brain, lung, pancreas and PBMC) using the PCR-subtraction protocol of Clontech, described above. The determined cDNA sequences of 90 clones isolated from this library are provided in SEQ ID NO: 316-404. Comparison of these sequences with those in the public database, as described above, revealed no significant homologies to the sequence of SEQ ID NO: 366. The sequences of SEQ ID NO: 321-325, 343, 354, 368, 369, 377, 382, 385, 389, 395, 397 and 400 were found to show some homology to previously isolated ESTs. The remaining sequences were found to show homology to previously identified gene sequences.

In yet further studies, a subtracted cDNA library (referred to as 2BT) was prepared from cDNA from breast tumors subtracted with a pool of cDNA from six normal tissues (liver, brain, stomach, small intestine, kidney and heart) using the PCR-subtraction protocol of Clontech, described above. cDNA clones isolated from this subtraction were subjected to DNA microarray analysis as described above and the resulting data subjected to four modified Gemtools analyses. The first analysis compared 28 breast tumors with 28 non-breast normal tissues. A mean over-expression of at least 2.1 fold was used as a selection cut-off. The second analysis compared 6

metastatic breast tumors with 29 non-breast normal tissues. A mean over-expression of at least 2.5 fold was used as a cut-off. The third and fourth analyses compared 2 early SCID mouse-passaged with 2 late SCID mouse-passaged tumors. A mean over-expression in the early or late passaged tumors of 2.0 fold or greater was used as a cut-off. In addition, a visual analysis was performed on the microarray data for the 2BT clones. The determined cDNA sequences of 13 clones identified in the visual analysis are provided in SEQ ID NO: 427-439. The determined cDNA sequences of 22 clones identified using the modified Gemtools analysis are provided in SEQ ID NO: 440-462, wherein SEQ ID NO: 453 and 454 represent two partial, non-overlapping, sequences of the same clone.

Comparison of the clone sequences of SEQ ID NO: 436 and 437 (referred to as 263G6 and 262B2) with those in the public databases, as described above, revealed no significant homologies to previously identified sequences. The sequences of SEQ ID NO: 427, 429, 431, 435, 438, 441, 443, 444, 445, 446, 450, 453 and 454 (referred to as 266B4, 266G3, 264B4, 263G1, 262B6, 2BT2-34, 2BT1-77, 2BT1-62, 2BT1-60,61, 2BT1-59, 2BT1-52 and 2BT1-40, respectively) showed some homology to previously isolated expressed sequences tags (ESTs). The sequences of SEQ ID NO: 428, 430, 432, 433, 434, 439, 440, 442, 447, 448, 449, 451, 452 and 455-462 (referred to as clones 22892, 22890, 22883, 22882, 22880, 22869, 21374, 21349, 21093, 21091, 21089, 21085, 21084, 21063, 21062, 21060, 21053, 21050, 21036, 21037 and 21048, respectively), showed some homology to gene sequences previously identified in humans.

EXAMPLE 2

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES OBTAINED BY PCR-BASED SUBTRACTION USING SCID-PASSAGED TUMOR RNA

Human breast tumor antigens were obtained by PCR-based subtraction using SCID mouse passaged breast tumor RNA as follows. Human breast tumor was implanted in SCID mice and harvested on the first or sixth serial passage, as described

in Patent Application Serial No. 08/556,659 filed 11/13/95, U.S. Patent No. 5,986,170. Genes found to be differentially expressed between early and late passage SCID tumor may be stage specific and therefore useful in therapeutic and diagnostic applications. Total RNA was prepared from snap frozen SCID passaged human breast tumor from both the first and sixth passage.

PCR-based subtraction was performed essentially as described above. In the first subtraction (referred to as T9), RNA from first passage tumor was subtracted from sixth passage tumor RNA to identify more aggressive, later passage-specific antigens. Of the 64 clones isolated and sequenced from this subtraction, no significant homologies were found to 30 of these clones, hereinafter referred to as: 13053, 13057, 13059, 13065, 13067, 13068, 13071-13073, 13075, 13078, 13079, 13081, 13082, 13092, 13097, 13101, 13102, 13131, 13133, 13119, 13135, 13139, 13140, 13146-13149, and 13151, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 88-116, respectively. The isolated cDNA sequences of SEQ ID NO: 117-140 showed homology to known genes.

In a second PCR-based subtraction, RNA from sixth passage tumor was subtracted from first passage tumor RNA to identify antigens down-regulated over multiple passages. Of the 36 clones isolated and sequenced, no significant homologies were found to nineteen of these clones, hereinafter referred to as: 14376, 14377, 14383, 14384, 14387, 14392, 14394, 14398, 14401, 14402, 14405, 14409, 14412, 14414-14416, 14419, 14426, and 14427, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 141-159, respectively. The isolated cDNA sequences of SEQ ID NO: 160-174 were found to show homology to previously known genes.

Further analysis of human breast tumor antigens through PCR-based subtraction using first and sixth passage SCID tumor RNA was performed. Sixty three clones were found to be differentially expressed by a two or more fold margin, as determined by microarray analysis, i.e., higher expression in early passage tumor over late passage tumor, or vice versa.. Seventeen of these clones showed no significant homology to any known genes, although some degree of homology with previously

identified expressed sequence tags (ESTs) was found, hereinafter referred to as 20266, 20270, 20274, 20276, 20277, 20280, 20281, 20294, 20303, 20310, 20336, 20341, 20941, 20954, 20961, 20965 and 20975 (SEQ ID NO: 252-268, respectively). The remaining clones were found to share some degree of homology to known genes, which are identified in the Brief Description of the Drawings and Sequence Identifiers section above, hereinafter referred to as 20261, 20262, 20265, 20267, 20268, 20271, 20272, 20273, 20278, 20279, 20293, 20300, 20305, 20306, 20307, 20313, 20317, 20318, 20320, 20321, 20322, 20326, 20333, 20335, 20337, 20338, 20340, 20938, 20939, 20940, 20942, 20943, 20944, 20946, 20947, 20948, 20949, 20950, 20951, 20952, 20957, 20959, 20966, 20976, 20977 and 20978. The determined cDNA sequences for these clones are provided in SEQ ID NO: 269-314, respectively.

The clones 20310, 20281, 20262, 20280, 20303, 20336, 20270, 20341, 20326 and 20977 (also referred to as B820P, B821P, B822P, B823P, B824P, B825P, B826P, B827P, B828P and B829P, respectively) were selected for further analysis based on the results obtained with microarray analysis. Specifically, microarray data analysis indicated at least two- to three-fold overexpression of these clones in breast tumor RNA compared to normal tissues tested. Subsequent studies led to the determination of the complete insert sequence for the clones B820P, B821P, B822P, B823P, B824P, B825P, B826P, B827P, B828P and B829P. These extended cDNA sequences are provided in SEQ ID NO: 416-426, respectively.

EXAMPLE 3

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol

(40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 4

ELICITATION OF BREAST ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of the breast-specific antigen B726P to elicit a cytotoxic T lymphocyte (CTL) response in peripheral blood lymphocytes from normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of a normal donor by growth for five days in RPMI medium containing 10% human serum, 30 ng/ml GM-CSF and 30 ng/ml IL-4. Following five days of culture, DC were infected overnight with adenovirus expressing recombinant B726P (downstream ORF; SEQ ID NO: 181) at an M.O.I. of 2.5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. CD8 positive cells were enriched for by the depletion of CD4 and CD14-positive cells. Priming cultures were initiated in individual wells of several 96-well plates with the cytokines IL-6 and IL-12. These cultures were restimulated in the presence of IL-2 using autologous fibroblasts treated with IFN-gamma and transduced with B726P and CD80. Following three stimulation cycles, the presence of B726P-specific CTL activity was assessed in IFN-gamma Elispot assays (Lalvani et al., *J. Exp. Med. 186*:859-865, 1997) using IFN-gamma treated autologous fibroblasts transduced to express either B726P or an irrelevant, control, antigen as antigen presenting cells (APC). Of approximately 96 lines, one line (referred to as 6-2B) was identified that appeared to specifically recognize B726P-transduced APC but not control antigen-transduced APC. This

microculture was cloned using standard protocols. B726P-specific CTL were identified by Elispot analysis and expanded for further analysis. These CTL clones were demonstrated to recognize B726P-expressing fibroblasts, but not the control antigen MART-1, using chromium-51 release assays. Furthermore, using a panel of allogeneic fibroblasts transduced with B726P in antibody blocking assays, the HLA restriction element for these B726P-specific CTL was identified as HLA-B*1501.

In order to define more accurately the location of the epitope recognized by the B726P-specific CTL clones, a deletion construct comprising only the N-terminal half of B726P (B726Pdelta3') was constructed (a.a. 1-129) into the pBIB retroviral expression plasmid. This plasmid as well as other plasmids containing B726P were transfected into COS-7 cells either alone or in combination with a plasmid expressing HLA-B*1501. Aproximately 48 hours after transfection, a B726P-specific CTL clone (1-9B) was added at approximately 10e4 cells per well. The wells were harvested the next day and the amount of IFN-gamma released was measured by ELISA. The CTL responded above background (EGFP) to COS-7 cells that had been transfected with both B726P and HLA-B*1501. There was no response above background to COS-7 cells that had been transfected with B726P or HLA-B*1501 only. Importantly, a higher response was seen with COS-7 cells that had been transfected with HLA-B*1501 and B726Pdelta3'. This result indicated that the epitope was likely to be located in the N-terminal region (a.a. 1-129) of B726P. This region was examined and amino acid sequences that corresponded to the HLA-B*1501 peptide binding motif (J. Immunol.1999,162:7277-84) were identified and synthesized. These peptides were pulsed at 10 ug/ml onto autologous B-LCL overnight. The next day the cells were washed and the ability of the cells to stimulate the B726P-specific CTL clone 1-9B was assayed in a IFN-gamma ELISPOT assay. Of the eleven peptides tested, only one peptide, having the amino acid sequence SLTKRASQY (a.a. 76-84; SEQ ID NO: 488) was able to be recognized by the CTL. This result identifies this peptide as being a naturally-processed epitope recognized by this B726P-specific CTL clone.

EXAMPLE 5

PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST BREAST TUMOR POLYPEPTIDES

Polyclonal antibodies against the breast tumor antigen B726P were prepared as follows.

The downstream ORF of B726P (SEQ ID NO: 181) expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37 °C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin, such as HiPrepQ (Biorad), was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The protein was then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of B726P antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4 °C for 12-24 hours followed by centrifugation.

Ninety-six well plates were coated with B726P antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 Microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H_2SO_4 and read immediately at 450 nm. The polyclonal antibodies showed immunoreactivity to B726P.

EXAMPLE 6

PROTEIN EXPRESSION OF BREAST TUMOR ANTIGENS

The downstream ORF of B726P (SEQ ID NO: 181), together with a C-terminal 6X His Tag, was expressed in insect cells using the baculovirus expression system as follows.

The cDNA for the full-length downstream ORF of B726P was PCR amplified using the primers of SEQ ID NO: 480 and 481. The PCR product with the expected size was recovered from agarose gel, restriction digested with EcoRI and Hind II, and ligated into the transfer plasmid pFastBac1, which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBB726P was used to make recombinant bacmid DNA and virus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies, Gaithersburg, MD). High Five cells were infected with the recombinant virus BVB726P to produce protein. The cDNA and amino acid sequences of the expressed B726P recombinant protein are provided in SEQ ID NO: 482 and 483, respectively.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

1. An isolated polypeptide, comprising at least an immunogenic portion of a breast tumor protein, wherein 4the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 under moderately stringent conditions; and

(c) complements of sequences of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NOs: 176, 179, 181, 469-473, 475, 485, 487 and 488.

4. An isolated polynucleotide encoding at least 15 amino acid residues of a breast tumor protein, or a variant thereof that differs in one or more

substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484 and 486 or a complement of any of the foregoing sequences.

5. An isolated polynucleotide encoding a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484. 486 and 489 or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489.

7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 under moderately stringent conditions.

8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.

10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a breast tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489 or a complement of any of the foregoing polynucleotide sequences.

12. A fusion protein, comprising at least one polypeptide according to claim 1.

13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.

16. A fusion protein, comprising a first amino acid portion and a second amino acid portion wherein said first amino acid portion includes 9 or more

contiguous amino acids from mammaglobin as depicted by amino acids 1-93 of SEQ ID NO: 493; wherein said second amino acid portion includes 9 or more contiguous amino acids from B726P as depicted by SEQ ID NO: 475, SEQ ID NO: 469, or SEQ ID NO: 176; and wherein said first amino acid portion is connected to either the amino terminal or carboxy-terminal end of said second amino acid portion.

17. The fusion protein of claim 16 wherein said first amino acid portion is

selected from the group consisting of IDELKECFLNQTDETLSNVE (amino acids 59-78 of SEQ ID NO: 493); TTNAIDELKECFLNQ (amino acids 55-69 of SEQ ID NO: 493); SQHCYAGSGCPLLENVISKTI (amino acids 13-33 of SEQ ID NO: 493); EYKELLQEFIDDNATTNAID (amino acids 41-60 of SEQ ID NO: 493); KLLMVLMLA (amino acids 2-10 of SEQ ID NO: 493); QEFIDDNATTNAI (amino acids 47-59 of SEQ ID NO: 493); and LKECFLNQTDETL (amino acids 62-74 of SEQ ID NO: 493).

18. The fusion protein of claim 16 wherein said second amino acid portion

includes 9 or more contiguous amino acids encoded by the combined upstream and downstream open reading frame (ORF) of B726P as depicted in SEQ ID NO: 475.

19. The fusion protein of claim 16 wherein said second amino acid portion

includes 9 or more contiguous amino acids encoded by the upstream ORF of B726P as depicted in from SEQ ID NO: 469.

20. The fusion protein of claim 16 wherein said second amino acid portion

includes 9 or more contiguous amino acids encoded by the downstream ORF of B726P as depicted in SEQ ID NO: 176.

21. The fusion protein of claim 16 wherein said second amino acid portion includes 9 or more contiguous amino acids from the amino acid sequence depicted by amino acids 1-129 of SEQ ID NO: 475.

22. The fusion protein of claim 16 as depicted in SEQ ID NO: 493.

23. The fusion protein of claim 16 as depicted in SEQ ID NO: 494.

24. The fusion protein of claim 16 as depicted in SEQ ID NO: 495.

25. An isolated polynucleotide encoding a fusion protein according to claim 12 or claim 16.

26. The fusion protein of claim 16 wherein said first amino acid portion is connected to the N-terminus of said second amino acid portion.

27. The fusion protein of claim 16 wherein said first amino acid portion is connected to the C-terminus of said second amino acid portion.

28. An isolated polynucleotide encoding a fusion protein according to claim 12 or claim 16.

29. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 4;

(c) an antibody according to claim 11;

(d) a fusion protein according to claim 12 or claim 16; and

(e) a polynucleotide according to claim 28.

30. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 4;

(c) an antibody according to claim 11;

(d) a fusion protein according to claim 12 or claim 16; and

(e) a polynucleotide according to claim 28.

31. An immunogenic composition according to claim 30, wherein the immunostimulant is an adjuvant.

32. An immunogenic composition according to claim 30, wherein the immunostimulant induces a predominantly Type I response.

33. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 29.

34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 30.

35. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

36. A pharmaceutical composition according to claim 29, wherein the antigen presenting cell is a dendritic cell or a macrophage.

37. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs:1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486, and 489-492;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);

in combination with an immunostimulant.

38. An immunogenic composition according to claim 37, wherein the immunostimulant is an adjuvant.

39. An immunogenic composition according to claim 37, wherein the immunostimulant induces a predominantly Type I response.

40. An immunogenic composition according to claim 37, wherein the antigen-presenting cell is a dendritic cell.

41. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii)encoded by a polynucleotide recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

and thereby inhibiting the development of a cancer in the patient.

42. A method according to claim 41, wherein the antigen-presenting cell is a dendritic cell.

43. A method according to any one of claims 33, 34 and 41, wherein the cancer is breast cancer.

44. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

45. A method according to claim 44, wherein the biological sample is blood or a fraction thereof.

46. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 44.

47. A method for stimulating and/or expanding T cells specific for a breast tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

(b) polynucleotides encoding a polypeptide of (a); and

(c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

48. An isolated T cell population, comprising T cells prepared according to the method of claim 47.

49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 49.

50. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that expresses a polypeptide of (i);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

51. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that express a polypeptide of (i);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

52. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

53. A method according to claim 52, wherein the binding agent is an antibody.

54. A method according to claim 53, wherein the antibody is a monoclonal antibody.

55. A method according to claim 52, wherein the cancer is breast cancer.

56. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

57. A method according to claim 56, wherein the binding agent is an antibody.

58. A method according to claim 57, wherein the antibody is a monoclonal antibody.

59. A method according to claim 56, wherein the cancer is a breast cancer.

60. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

61. A method according to claim 60, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

62. A method according to claim 60, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

63. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-175, 178, 180, 182-468, 474, 476, 477, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

64. A method according to claim 63, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

65. A method according to claim 63, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

66. A diagnostic kit, comprising:

(a) one or more antibodies according to claim 11; and

(b) a detection reagent comprising a reporter group.

67. A kit according to claim 66, wherein the antibodies are immobilized on a solid support.

68. A kit according to claim 66, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

69. A kit according to claim 66, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

70. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325,

343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489-492 or a complement of any of the foregoing polynucleotides.

71. A oligonucleotide according to claim 70, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NOs: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 321-325, 343, 354, 367-369, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454, 463-468, 474, 479, 484, 486 and 489-492.

72. A diagnostic kit, comprising:

(a) an oligonucleotide according to claim 71; and

(b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

SYN18C6 NORTHERN BLOT

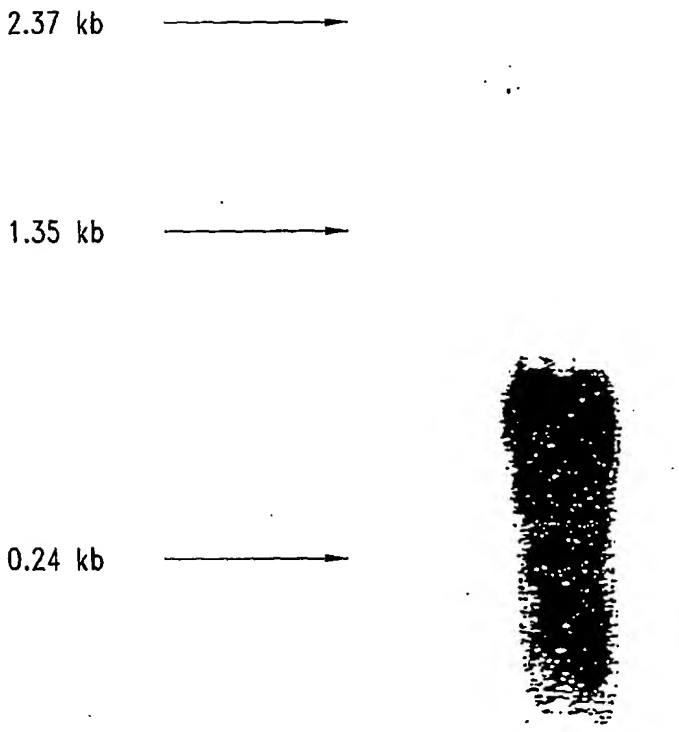

Fig. 1

SEQUENCE LISTING

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Mitcham, Jennifer L.
Xu, Jiangchun
Harlocker, Susan L.
Hepler, William T.

<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF BREAST CANCER

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<400> 23
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ttgttgtaac ttaaggtatc ttgctacagt agacagaatt ggtaatagca acttttaaaa 240
ttgtcattag ttctgcaata ttagctgaaa tgtagtacag aaaagaatgt acatttagac 300
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acatatggac ctcccgggcg g 381

<210> 24
<211> 214
<212> DNA
<213> Homo sapien

<400> 24
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tccacaaata ctgaggtata gcctgcatgc cactaaaaat aacaaaggtt tcaggggtgg 180
aaacattgtc caccacactg tcatgaccat cttt 214

<210> 25
<211> 302
<212> DNA
<213> Homo sapien

<400> 25
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ac 302

<210> 26
<211> 301
<212> DNA
<213> Homo sapien

<400> 26
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gccaggatct gggcctgttt cttcccttct gccacattga tggccgactc tcgggtcccc 240
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t 301

<210> 27
<211> 301
<212> DNA
<213> Homo sapien

<400> 27
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tcaaattgaa atcatcttcc ctctgtacag attgcaatat ctgataatac cctcaacttt 180
cttggtgcaa attaattgcc tggtactcac agtccagtgt taacaggcaa taatggtgtg 240
attccagagg agaggactag gtggcaggaa aataaatgag attagcagta tttgacttgg 300
a 301

<210> 28
<211> 286
<212> DNA
<213> Homo sapien

<400> 28
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gtcccttgtt caccaaatgg tcaaagggtc aaagatcgga ggaggtcagg gggtaacgca 180
ggaacaggtg agggcgtttc gccctctctc cctctcccct tttcaacctc ttaatcactg 240
gctaactcgc gacctcatgg gttaattcgt aagcttacac gcgttg 286

<210> 29
<211> 301
<212> DNA
<213> Homo sapien

<400> 29
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a 301

<210> 30
<211> 332
<212> DNA
<213> Homo sapien

<400> 30
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ccaggcaatt aatttgcacc aagaaagttg agggtattat cagatattgc aatctgtaca 180
gagggaagat gatttcaatt tgatttcaac ttaaccttca tctttgtctg ttaacactaa 240
tagagggtgt ctaataaaat ggtcaaattt gtgatctcat ttgttataac tagcactctt 300
ttcacagatg tgatgactga tttccagcag ac 332

<210> 31
<211> 141
<212> DNA
<213> Homo sapien

<400> 31
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tttcatttgc aggggttcag ggagggttgc aggggttcag ggagggctct tgtcccacaa 120
ccgggggaag ggagagggca c 141

<210> 32
<211> 201
<212> DNA
<213> Homo sapien

<400> 32
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aatctgtcat ctaccttaaa gagagaaaaa agatggaaca taggcccacc tagtttcatc 120
catccaccta cataaccaac atagatgtga ggtccactgc actgatagcc agactgcctg 180
gggtaaacct tttcagggag g 201

<210> 33
<211> 181
<212> DNA
<213> Homo sapien

<400> 33
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gactaaactt caagtcacag acttttatgt gacagattgg agcagggttt gttatgcatg 120

tagagaaccc aaactaattt attaaacagg atagaaacag gctgtctggg tgaaatggtt 180
c 181

<210> 34
<211> 151
<212> DNA
<213> Homo sapien

<400> 34
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catttctcct caccacgggg tcgcttgtca gctccaagaa ccagtctggc cccactgaga 120
acttttcagt cgagggcctg atgaatcttg g 151

<210> 35
<211> 291
<212> DNA
<213> Homo sapien

<400> 35
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tttcagtttg tttttcacct ataatgaatt gtaaaaacaa acatacttgt ggggtctgat 180
agcaaacata gaaatgatgt atattgtttt ttgttatcta tttattttca tcaatacagt 240
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<210> 36
<211> 201
<212> DNA
<213> Homo sapien

<400> 36
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aaattttgtt tacatgaata tggaataaat acaataatca aaatatgact ctccctaaaa 120
gtgaaacaca caagccaatc cggaactgct gtgcgaaaga taaaatcgag aaaggcaagg 180
tttcggtagg aggacgcgat g 201

<210> 37
<211> 121
<212> DNA
<213> Homo sapien

<400> 37
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cgtattacaa ttcactggcc gtcgttttac aacgtcgtga ctgggaaaac cctggcgtta 120
c 121

<210> 38
<211> 200
<212> DNA
<213> Homo sapien

<400> 38
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gataacacca cacatagaac attataatta cacacaaatt tatggtaaaa gaattaatat 180
gctgtctggt gctgctgtta 200

<210> 39
<211> 760
<212> DNA
<213> Homo sapien

<400> 39
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gtaaatactg tttggtttgt tcagacctgc ccgggcggcc 760

<210> 40
<211> 452
<212> DNA
<213> Homo sapien

<400> 40
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ggtttatcgt gacttttcct tcttgtttac ttttcgctag gaaggggagt tgtagggca 180
gattcaggta ttggaatagg aaaattacgt ctaaaccatg gaaatcttgg aaatggaatt 240
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gccactgcca agatggctgt gatcaggagg agaactttct tcatctcaaa cgtttcagtc 420
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<210> 41
<211> 676
<212> DNA
<213> Homo sapien

<400> 41
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aagatacata gcaatgatag caggtttctt tttaaagctt agtattaata ttaaatattt 120
ttccccattt aaattttaca ttacttgcca agaaaaaaaa aaaattaaaa ctcaagttac 180
ttgaagcctg gacacacttc catgattagc cgggctaggt aaaagttggt ggctttattc 240
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tgggctgaag cttggttggt actgaattct ctaagaggtt tcttctagaa acagacaact 660
cagacctgcc cgggcg 676

<210> 42
<211> 468
<212> DNA
<213> Homo sapien

<400> 42
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gtaagactcg ggattagtac acacttgttg attaatggaa atgtttacag atccccaagc 240
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aaaaccccct gcaaagccca gcttgaaacc ttcacttagg aacgtaatcg tgtcccctat 420

cctacttccc cttcctaatt ccacagacct gcccgggcgg ccgctcga 468

<210> 43
<211> 408
<212> DNA
<213> Homo sapien

<400> 43
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ttcatttcag gagagcagca gttaaacccg tggattttgt agttaggaac ctgggttcaa 120
acctctttcc actaattggc tatgtctctg gacagttttt ttttttttt ttttttttaa 180
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taaggctgta agagtctaaa acctacagtg aatcacaatg catttacccc cactgacttg 360
gacataagtg aaaactagcc cgaagtctct ttttcaaatt acttacag 408

<210> 44
<211> 160
<212> DNA
<213> Homo sapien

<400> 44
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ctctctgtgc tacaatgatt gcaccttctc acgcaacact ccaaccagga ctttcaacta 120
caacttctcc gctttggcaa acaccgtcac tcttgctgga 160

<210> 45
<211> 231
<212> DNA
<213> Homo sapien

<400> 45
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ccccaataag tcgatcagca aggctgacag gctgtgagga aaccccggcc ttgtagcctg 120
tcacctctgg ggggatgatg actgcctggc agacgtaggc tgtgatagat ttgggagaaa 180
acctgactca ccctcaggaa tccggaggtc ggtgacattg tcggtgcaca c 231

<210> 46
<211> 371
<212> DNA
<213> Homo sapien

<400> 46
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ctgtatatgc agaatctttt ccctaaatac tgcttcgtcc catgtctgaa ggcgtaaaat 180
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tcaattgcct t 371

<210> 47
<211> 261
<212> DNA
<213> Homo sapien

<400> 47
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gcaggattcg atgagattga gcaagatctt actcagagat ttgaagaaaa gctgcaggaa 180
ctagaaagtg tttccaggga tcccagcaat gagaatccta aacttgaaga cctctgcttc 240
atcttacaag aagagtacca c 261

<210> 48
<211> 701
<212> DNA
<213> Homo sapien

<400> 48
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tgtagtgcca ttagaaactg tgaatttcca aataaatttg a 701

<210> 49
<211> 270
<212> DNA
<213> Homo sapien

<400> 49
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ggatgaaaac ttgcatagaa ttctgattaa atagtgggtc tgtttcacat gtgcagtttg 240
aagtatttaa attaaccact cctttcacag 270

<210> 50
<211> 271
<212> DNA
<213> Homo sapien

<400> 50
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<210> 51
<211> 241
<212> DNA
<213> Homo sapien

<400> 51
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ccagctcctg ctgcagttat tcctacagaa gctgccattt accagccctc tgtgattttg 180
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t 241

<210> 52
<211> 271
<212> DNA
<213> Homo sapien

<400> 52

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gtgtagacaa acttcccctg aatttgctag a 271

<210> 53
<211> 493
<212> DNA
<213> Homo sapien

<400> 53
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cctcaagggc gaattctgca gatatccatc acactggcgg ccgctcgagc atgcatctag 480
agggcccaat tcg 493

<210> 54
<211> 321
<212> DNA
<213> Homo sapien

<400> 54
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actgaatgtc aataaactct gtgattttgt taggaagtaa aactgggatc tatttagcca 120
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gactttctct ctggagatac ccttttgaat atacaatggc cttggctcac taggtttaaa 240
tacaaacaag tctgaaaccc actgaagact gagagattgc agcaatattc tctgaattag 300
gatcgggttc cataactcta a 321

<210> 55
<211> 281
<212> DNA
<213> Homo sapien

<400> 55
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attaacatgc cacacgaaga ctgcattaca gctctctgtt tctgtaatgc agaaaaatct 120
gaacagccca ccttggttac agctagcaaa gatggttact tcaaagtatg gatattaaca 180
gatgactctg acatatacaa aaaagctgtt ggctggacct gtgactttgt tggtagttat 240
cacaagtatc aagcaactaa ctgttgtttc tccgaagatg g 281

<210> 56
<211> 612
<212> DNA
<213> Homo sapien

<400> 56
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gggcggccgt cg 612

<210> 57
<211> 363
<212> DNA
<213> Homo sapien

<400> 57
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gacaagacat ttgacttccc tttctccttg tctataaaat gtggacagtg gacgtctgtc 120
acccaagaga gttgtgggag acaagatcac agctatgagc acctcgcacg gtgtccagga 180
tgcacagcac aatccatgat gcgttttctc cccttacgca ctttgaaacc catgctagaa 240
aagtgaatac atctgactgt gctccactcc aacctccagc gtggatgtcc ctgtctgggc 300
ccttttctg ttttttattc tatgttcagc accactggca ccaaatacat tttaattcac 360
cga 363

<210> 58
<211> 750
<212> DNA
<213> Homo sapien

<400> 58
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cacaaaggtg cccatcaagc gctcagaaat gctgagagat atcatccgtg aatacactga 240
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caagatggga ctgcgtcctg gggtgagaca tcccctccct tggagatcta aggaaacttc 540
tcacctatga gtttgtaaag cagaaatacc tggactacag acgagtgccc aacagcaacc 600
ccccggagta tgagttcctc tggggcctcc gtccctacca tgagactagc aagatgaaaa 660
tgctgagatt cattgcagag gttcagaaaa gagaccctcg tgactggact gcacagttca 720
tggaggctgc agatgaggac ctgcccgggc 750

<210> 59
<211> 505
<212> DNA
<213> Homo sapien

<400> 59
tggccgcccg ggcaggtcca gtctacaagc agagcactct catggggagc accagatgag 60
ttccagccgc agttctttta taagctttaa gtgcctcatg aagacgcgag gatctcttcc 120
aagtgcaacc tggtcacatc agggcacatt cagcagcaga agtctgtttc cagtatagtc 180
cttggtatgg ctaaattcca ctgtcccttt ctcagcagtc aataatccat gataaattct 240
gtacaacact gtagtcaata acagcagcac cagacagcat attaattctt ttaccataaa 300
tttgtgtgta attataatgt tctatgtgtg gtgttatcaa aagaatcact gtgtctctaa 360
atatcatata tgtatgtctg gataaataca ttgctgtaca acatctccaa catgcaggtc 420
atgctctaag acttggggat atagagtaat acatgtttcg tggacctcgg ccgcgaccac 480
gctaagggcg aattctgcag atatc 505

<210> 60
<211> 520
<212> DNA
<213> Homo sapien

<400> 60
cgtggtcgcg gccgaggtcc tcaggacaag gaaacaggta tcagcatgat ggtagcagaa 60
accttatcac caaggtgcag gagctgactt cttccaaaga gttgtggttc cgggcagcgg 120
tcattgcctg cccttgctgg agggctgatt ttagtgttgc ttattatgtt ggccctgagg 180

atgcttcgaa gtgaaaataa gaggctgcag gatcagcggc aacagatgct ctcccgtttg 240
cactacagct ttcacggaca ccattccaaa aaggggcagg ttgcaaagtt agacttggaa 300
tgcatggtgc cggtcagtgg gcacgagaac tgctgtctga cctgtgataa aatgagacaa 360
gcagacctca gcaacgataa gatcctctcg cttgttcact ggggcatgta cagtgggcac 420
gggaagctgg aattcgtatg acggagtctt atctgaacta cacttactga acagcttgaa 480
ggacctgccc gggcggccgc tcgaaagggg cgaattctgc 520

<210> 61
<211> 447
<212> DNA
<213> Homo sapien

<400> 61
agagaggtgt ttttattctt tggggacaaa gccgggttct gtgggtgtag gattctccag 60
gttctccagg ctgtagggcc cagaggctta atcagaattt tcagacaaaa ctggaacctt 120
tctttttcc cgttggttta tttgtagtcc ttgggcaaac caatgtcttt gttcgaaaga 180
gggaaaataa tccaaacgtt tttcttttaa ctttttttt aggttcaggg gcacatgtgt 240
aggcttgcta tataggtaaa ttgcatgtca ccagggtttg ttgtacagat tatttcatca 300
tccagataaa aagcatagta ccagataggt agtttttga tcctcaccct ccttccatgc 360
tccgacctca ggtaggcccc agtgtctgac ctgcccggcg gcccgctcga aagggccaat 420
tctgcagata tccatcacac tggccgg 447

<210> 62
<211> 83
<212> PRT
<213> Homo sapien

<400> 62
Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
1 5 10 15
Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser Asp
20 25 30
Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
35 40 45
Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
50 55 60
Arg Asn Phe Pro Ile Pro Ile Pro Ser Ala Pro Thr Thr Pro Leu Pro
65 70 75 80
Ser Glu Lys

<210> 63
<211> 683
<212> DNA
<213> Homo sapien

<400> 63
acaaagattg gtagctttta tatttttta aaaatgctat actaagagaa aaaacaaaag 60
accacaacaa tattccaaat tataggttga gagaatgtga ctatgaagaa agtattctaa 120
ccaactaaaa aaaatattga aaccactttt gattgaagca aaatgaataa tgctagattt 180
aaaaacagtg tgaaatcaca ctttggtctg taaacatatt tagctttgct tttcattcag 240
atgtatacat aaacttattt aaaatgtcat ttaagtgaac cattccaagg cataataaaa 300
aaagwggtag caaatgaaaa ttaaagcatt tattttggta gttcttcaat aatgatrcga 360
gaaactgaat tccatccagt agaagcatct ccttttgggt aatctgaaca agtrccaacc 420
cagatagcaa catccactaa tccagcacca attccttcac aaagtccttc cacagaagaa 480
gtgcgatgaa tattaattgt tgaattcatt tcagggcttc cttggtccaa ataaattata 540
gcttcaatgg gaagaggtcc tgaacattca gctccattga atgtgaaata ccaacgctga 600
cagcatgcat ttctgcattt tagccgaagt gagccactga acaaaactct tagagcacta 660
tttgaacgca tctttgtaaa tgt 683

<210> 64
<211> 749

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(749)
<223> n = A,T,C or G

<400> 64
ctgttcattt gtccgccagc tcctggactg gatgtgtgaa aggcatcaca tttccatttt 60
cctccgtgta aatgttttat gtgttcgcct actgatccca ttcgttgctt ctattgtaaa 120
tatttgtcat ttgtatttat tatctctgtg ttttcccct aaggcataaa atggtttact 180
gtgttcattt gaacccattt actgatctct gttgtatatt tttcatgcca ctgctttgtt 240
ttctcctcag aagtcgggta gatagcattt ctatcccatc cctcacgtta ttggaagcat 300
gcaacagtat ttattgctca gggtcttctg cttaaaactg aggaaggtcc acattcctgc 360
aagcattgat tgagacattt gcacaatcta aaatgtaagc aaagtaagtc attaaaaata 420
caccctctac ttgggcttta tactgcatac aaatttactc atgagccttc ctttgaggaa 480
ggatgtggat ctccaaataa agatttagtg tttattttga gctctgcatc ttancaagat 540
gatctgaaca cctctccttt gtatcaataa atagccctgt tattctgaag tgagaggacc 600
aagtatagta aaatgctgac atctaaaact aaataaatag aaaacaccag gccagaacta 660
tagtcatact cacacaaagg gagaaattta aactcgaacc aagcaaaagg cttcacggaa 720
atagcatgga aaaacaatgc ttccagtgg 749

<210> 65
<211> 612
<212> DNA
<213> Homo sapien

<400> 65
acagcagcag tagatggctg caacaacctt cctcctaccc cagcccagaa aatatttctg 60
ccccacccca ggatccggga ccaaaataaa gagcaagcag gccccttca ctgaggtgct 120
gggtagggct cagtgccaca ttactgtgct ttgagaaaga ggaaggggat ttgtttggca 180
ctttaaaaat agaggagtaa gcaggactgg agaggccaga gaagatacca aaattggcag 240
ggagagacca tttggcgcca gtcccctagg agatgggagg agggagatag gtatgagggt 300
aggcgctaag aagagtagga ggggtccact ccaagtggca gggtgctgaa atgggctagg 360
accaacagga cactgactct aggtttatga cctgtccata cccgttccac agcagctggg 420
tgggagaaat caccattttg tgacttctaa taaaataatg ggtctaggca acagttttca 480
atggatgcta aaacgattag gtgaaaagtt gatggagaat tttaattcag gggaattagg 540
ctgataccat ctgaaaccat ttggcatcat taaaaatgtg acaacctggt ggctgccagg 600
gaggaagggg ag 612

<210> 66
<211> 703
<212> DNA
<213> Homo sapien

<400> 66
tagcgtggtc gcggccgagg tacattgatg ggctggagag cagggttggc agcctgttct 60
gcacagaacc aagaattaca gaaaaaagtc caggagctgg agaggcacaa catctccttg 120
gtagctcagc tccgccagct gcagacgcta attgctcaaa cttccaacaa agctgcccag 180
accagcactt gtgttttgat tcttcttttt tccctggctc tcatcatcct gcccagcttc 240
agtccattcc agagtcgacc agaagctggg tctgaggatt accagcctca cggagtgact 300
tccagaaata tcctgaccca caaggacgta acagaaaatc tggagaccca agtggtagag 360
tccagactga gggagccacc tggagccaag gatgcaaatg gctcaacaag gacactgctt 420
gagaagatgg gagggaagcc aagacccagt gggcgcatcc ggtccgtgct gcatgcagat 480
gagatgtgag ctggaacaga ccttcctggc ccacttcctg atcacaagga atcctgggct 540
tccttatggc tttgcttccc actgggattc ctacttaggt gtctgccctc aggggtccaa 600
atcacttcag gacaccccaa gagatgtcct ttagtctctg cctgaggcct agtctgcatt 660
tgtttgcata tatgagaggg tacctgcccg ggcggccgct cga 703

<210> 67
<211> 1022

<212> DNA
<213> Homo sapien

<400> 67
cttgagaaag caggattgtt ttaagttcca agatttaaca aacttactgt tcagcatcat 60
attcaagcct aaaaggaaga taggattttc aagatatatt tccaacttct ttaacatggc 120
accatggatg aactgtttct cagcactgtg ctgcttcact tggaattaag gatgaattgg 180
gaggagacag tatgacatag gtgggtaggt tgggtggtga ggggaaccag ttctaatagt 240
cctcaactcc actccagctg ttcctgttcc acacggtcca ctgagctggc ccagtccctt 300
tcactcagtg tgtcaccaaa ggcagcttca aggctcaatg gcaagagacc acctataacc 360
tcttcacctt ctgctgcctc tttctgctgc cactgactgc catggccatc tgctatagcc 420
gcattgtcct cagtgtgtcc aggccccaga caaggaaggg gagccatggt gagactccaa 480
ttcccaggcc ttaatcctta accctagacc tgttgcctct agcatcattt atttatctac 540
ctacctaata gctatctacc agtcattaaa ccatggtgag attctaacca tgtctagcac 600
ctgatgctag agataatttt gttgaatccc ttcaattata aacagctgag ttagctggac 660
aaggactagg gaggcaatca gtattattta ttcttgaaca ccatcaagtc tagacttggt 720
ggcttcatat ttctatcata atccctgggg gtaagaaatc atatagcccc aggttgggaa 780
ggggaaaacg gtttgcaaca ttctcctcct tgtaggaggc gagctctgtc tcactagcta 840
tgcccctcca tcaattcacc ctatactcag atcagaagct gagtgtctga attacagtat 900
attttctaaa ttcctagccc ctgctggtga atttgccctc ccccgctcct ttgacaattg 960
tccccgtgtt cgtctccggg ccctgagact ggccctgctt atcttgctga ccttcatcct 1020
ct 1022

<210> 68
<211> 449
<212> DNA
<213> Homo sapien

<400> 68
ccagatccat tttcagtggt ctggatttct ttttattttc ttttcaactt gaaagaaact 60
ggacattagg ccactatgtg ttgttactgc cactagtgtt caagtgcctc ttgttttccc 120
agagatttcc tgggtctgcc agaggcccag acaggctcac tcaagctctt taactgaaaa 180
gcaacaagcc actccaggac aaggttcaaa atggttacaa cagcctctac ctgtcgcccc 240
agggagaaag gggtagtgat acaagtctca tagccagaga tggttttcca ctccttctag 300
atattcccaa aaagaggctg agacaggagg ttattttcaa ttttattttg gaattaaata 360
ctttttccc tttattactg ttgtagtccc tcacttggat atacctctgt tttcacgata 420
gaaataaggg aggtctagag cttctattc 449

<210> 69
<211> 387
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(387)
<223> n = A,T,C or G

<400> 69
gcccttagcg tgggtcgcgg cncgangtct ggagcntatg tgatncctat ggtncncagg 60
cnnatactgc tantctcatt tattctcctg cnacctantc ctctnctctg gaatcacacc 120
attattgcct gttaacactg gactgtgagt accangcaat taatttgcac caanaaagtt 180
gagggtatta tcanatattg caatctgtac agagggaaga tgatttcaat ttgatttcaa 240
cttaaccttc atctttgtct gttaacacta atagagggtg tctaataaaa tggcaaattt 300
gngatctcat tnggtataac tacactcttt ttcacagatg tgatgactga atttccanca 360
acctgcccgg gcggncgntc naagggc 387

<210> 70
<211> 836
<212> DNA
<213> Homo sapien

<400> 70
tattccattt acaaaataaa ttcagccctg cactttcttt agatgccttg atttccagaa 60
tggagcttag tgctactgaa taccctggcc acagagccac ctcaggatat tcttttctcc 120
accctagttt atttatttat agatatctgt ttacaaagtc tgtagtaaat cctgatgctg 180
accatctgaa atgtactttt tttctgaatg ctgtttcaat ctaaaatagc agcttttgag 240
aaaacaatga tgtaaattcc ttatgataaa aggatgattc tatatattct ttaatgatat 300
taaatatgcc gaagccaagc acacagtctt tctaaagtgt gtgtatgttt gtgtgaatgt 360
gaatgatact gatcttatat ctgttaaaag ttgttttaaa aagctgtggc atcccattgt 420
tcatatttgc caagtcttct gtaaagatgt ctaggacgaa atattttatg tgctaatgca 480
tgtatttgta aaccagattt gtttaccact caaaattaac ttgttttctt catccaaaaa 540
agtttatttc ttccacgtac ttaaattttc tgtgtgggta taatatagct ttctaatttt 600
tttctttcac aaaggcaggt tcaaaattct gttgaaagaa aaatgctttc tgaaactgag 660
gtataacacc agagcttgct gtttaaagga ttatatgatg tacatcagtt ctataaatgt 720
gctcagcagt ttaacatgtg aatcctgttt taaagtgctc agatttcaac tgtgtaagcc 780
attgatataa cgctgtaatt aaaaatgttt atatgaaaaa aaaaaaaaaa aaaaaa 836

<210> 71
<211> 618
<212> DNA
<213> Homo sapien

<400> 71
gttgcagtga gctcaagtgt tgggtgtatc agctcaaaac accatgtgat gccaatcatc 60
tccacaggag caatttgttt acctttttt tctgatgctt tactaacttc atcttttaga 120
tttaaatcat tagtagatcc tagaggagcc agtttcagaa aatatagatt ctagttcagc 180
accacccgta gttgtgcatt gaaataatta tcattatgat tatgtatcag agcttctggt 240
tttctcattc tttattcatt tattcaacaa ccacgtgaca aacactggaa ttacaggatg 300
aagatgagat aatccgctcc ttggcagtgt tatactatta tataacctga aaaaacaaac 360
aggtaatttt cacacaaagt aatagatatc atgacacatt taaaataggg cactactgga 420
acacacagat aggacatcca ggttttgggt caatattgta gacttttgg tggatgagat 480
atgcaggttg atrccagaag gacaacaaaa acatatgtca gatagaaggg aggagcaaat 540
gccaagagct ggagctgagg aagatcactg tgaaattcta tgtagtctag ttggctggat 600
gctagagcaa agaggtgg 618

<210> 72
<211> 806
<212> DNA
<213> Homo sapien

<400> 72
tctacgatgg ccatttgctc attgtctttc ctctgtgtgt agtgagtgac cctggcagtg 60
tttgcctgct cagagtggcc cctcagaaca acagggctgg ccttggaaaa accccaaaac 120
aggactgtgg tgacaactct ggtcaggtgt gatttgacat gagggccgga ggcggttgct 180
gacggcagga ctggagaggc tgcgtgcccg gcactggcag cgaggctcgt gtgtccccca 240
ggcagatctg ggcactttcc caacccaggt ttatgccgtc tccagggaag cctcggtgcc 300
agagtggtgg gcagatctga ccatccccac agaccagaaa caaggaattt ctgggattac 360
ccagtccccc ttcaacccag ttgatgtaac cacctcattt tttacaaata cagaatctat 420
tctactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcatgc 480
tccgggcccc acgtggctcc tgtgctctag atcatggtga ctcccccgcc ctgtggttgg 540
aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg 600
ccctttaatg ggattgaaag cacttttacc acatggagaa atatattttt aatttgtgat 660
gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc 720
taatgaaagc tgatgaattt tcttttctgt ccaaacaagt aaaataaaaa taaaagtcta 780
tttagatgtt gaaaaaaaaa aaaaaa 806

<210> 73
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(301)
<223> n = A,T,C or G

<400> 73
actctggtaa gcttgttgtt gtccaagtga agctccctca gatgaggcgt gttggccana 60
gagccattgt caacagcaga gatgctgttg aaactcaatc ccaacttagc caaattattc 120
agtcctttca ggctagctgc atcaactctg ctgattttgt tgccatcaag atgtaattcc 180
gtaagggaag gaggaagacc ttgaggaatg ctggygatat tggyatcagc aatgcggatg 240
tasgaagagc ttcttcmttc cctggaaagc cccattttca atyccttgag ctcttcakcg 300
g 301

<210> 74
<211> 401
<212> DNA
<213> Homo sapien

<400> 74
agtttacatg atccctgtaa cagccatggt ctcaaactca gatgcttcct ccatctgcca 60
agtgtgttct ggatacagag cacatcgtgg cttctggggt cacactcagc ttaggctgtg 120
ggtccacaga gcactcatct ggctgggcta tggtggtggt ggctctactc aagaagcaaa 180
gcagttacca gcacattcaa acagtgtatt gaacatcttt taaatatcaa agtgagaaac 240
aagaaggcaa cataataatg ttatcagaaa gatgttagga agtaaggaca gctgtgtaaa 300
gcttgaggct gaaaagtagc ttgccagctt catttctttg gtttcttggg tagtgggccg 360
ccggaacagc aagatgtgag gttctggttc atggatcata t 401

<210> 75
<211> 612
<212> DNA
<213> Homo sapien

<400> 75
ttatttttca atttttattt tggttttctt acaaaggttg acattttcca taacaggtgt 60
aagagtgttg aaaaaaaaat tcaaattttt ggggagcgag ggaaggagtt aatgaaactg 120
tattgcacaa tgctctgatc aatccttctt tttctctttt gcccacaatt taagcaagta 180
gatgtgcaga agaaatggaa ggattcagct ttcagttaaa aaagaagaag aagaaatggc 240
aaagagaaag ttttttcaaa tttctttctt ttttaattta gattgagttc atttatttga 300
aacagactgg gccaatgtcc acaaagaatt cctggtcagc accaccgatg tccaaaggtg 360
caatatcaag gaagggcagg cgtgatggct tatttgtttt gtattcaatg attgtctttc 420
cccattcatt tgtcttttta gagcagccat ctacaagaac agtgtaagtg aacctgctgt 480
tgccctcagc aacaagttca acatcattag agccctgtag aatgacagcc tttttcaggt 540
tgccagtctc ctcatccatg tatgcaatgc tgttcttgca gtggtaggtg atgttctgag 600
aggcatagtt gg 612

<210> 76
<211> 844
<212> DNA
<213> Homo sapien

<400> 76
ggctttcgag cggccgcccg ggcaggtctg atggttctcg taaaaacccc gctagaaact 60
gcagagacct gaaattctgc catcctgaac tcaagagtgg agaatactgg gttgacccta 120
accaaggatg caaattggat gctatcaagg tattctgtaa tatggaaact ggggaaacat 180
gcataagtgc caatcctttg aatgttccac ggaaacactg gtggacagat tctagtgctg 240
agaagaaaca cgtttggttt ggagagtcca tggatggtgg ttttcagttt agctacggca 300
atcctgaact tcctgaagat gtccttgatg tgcagcykgc attccttcga cttctctcca 360
gccgagcttc ccagaacatc acatatcact gcaaaaatag cattgcatac atggatcagg 420
ccagtggaaa tgtaaagaag gccctgaagc tgatggggtc aaatgaaggt gaattcaagg 480
ctgaaggaaa tagcaaattc acctacacag ttctggagga tggttgcacg aaacacactg 540
gggaatggag caaaacagtc tttgaatatc gaacacgcaa tgctgttcct tgacattgca 600
ccaccaatgt ccagaggtgc aatgtcaagg aacggcaggc gagatggctt atttgttttg 660
tattcaatga ttgtcttgcc ccattcattt gtctttttgg agcagccatc gactaggaca 720
gagtaggtga acctgctgtt gccctcagca acaagttcca catcgttgga accctgcaga 780

agcacagcct tgttcaarct gcccgtctcc tcatccagat acctcggccg cgaccacgct 840
aatc 844

<210> 77
<211> 314
<212> DNA
<213> Homo sapien

<400> 77
ccagtcctcc acttggcctg atgagagtgg ggagtggcaa gggacgtttc tcctgcaata 60
gacacttaga tttctctctt gtgggaagaa accacctgtc catccactga ctcttctaca 120
ttgatgtgga aattgctgct gctaccacca cctcctgaag aggcttccct gatgccaatg 180
ccagccatcc tggcatcctg gccctcgagc aggctgcggt aagtagcgat ctcctgctcc 240
agccgtgtct ttatgtcaag cagcatcttg tactcctggt tctgagcctc catctcgcat 300
cggagctcac tcag 314

<210> 78
<211> 548
<212> DNA
<213> Homo sapien

<400> 78
accaagagcc aagtgttaca caggatattt taaaaataaa atgtttttgg aatcctcacc 60
tcccatgcta tcttctaaga taactacaaa tattcttcaa agatttaact gagttctgcc 120
aaggacctcc caggactcta tccagaatga ttattgtaaa gctttacaaa tcccaccttg 180
gccctagcga taattaggaa atcacaggca aacctcctct ctcggagacc aatgaccagg 240
ccaatcagtc tgcacattgg ttttgttaga tactttgtgg agaaaaacaa aggctcgtga 300
tagtgcagct ctgtgcctac agagagcctc ccttttggtt ctgaaattgc tgatgtgaca 360
gagacaaagc tgctatgggt ctaaaacctt caataaagta actaatgaca ctcaaggtcc 420
tgggactctg agacagacgg tggtaaaacc cacagctgcg attcacattt ccaatttatt 480
ttgagctctt tctgaagctg ttgcttccta cctgagaatt cccatttaga gagctgcaca 540
gcacagtc 548

<210> 79
<211> 646
<212> DNA
<213> Homo sapien

<400> 79
accccgtcac tatgtgaata aaggcagcta gaaaatggac tcaattctgc aagccttcat 60
ggcaacagcc catattaaga cttctagaac aagttaaaaa aaatcttcca tttccatcca 120
tgcatgggaa aagggcttta gtatagttta ggatggatgt gtgtataata ataaaatgat 180
aagatatgca tagtggggga ataaagcctc agagtccttc cagtatgggg aatccattgt 240
atcttagaac cgagggattt gtttagattg ttgatctact aatttttttc ttcacttata 300
tttgaatttt caatgatagg acttattgga aattggggat aattctgttg tggtattaaa 360
taatattcat tttttaaaaa ctcatcttgg tattgagtta gtgcattgac ttccaatgaa 420
ttgacataag cccatatttc attttaacca gaaacaaaaa ctagaaaatg ttactcccta 480
aataggcaac aatgtatttt ataagcactg cagagattta gtaaaaaaca tgtatagtta 540
ctttagaaac aacttctgac acttgagggt tacccaatgg tctccttccc attctttata 600
tgaggtaaat gcaaaccagg gagccaccga ataaacagcc ctgagt 646

<210> 80
<211> 276
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(276)
<223> n = A,T,C or G

<400> 80

gtctgaatga gcttcnctgc gagatgganc ancataaccc agaantccaa aancntanng 60
aacgnnaaaa cccgntngaa caagnaaacn gcaactnacg gccgcctgnt gnagggcgag 120
gacgcccacc tctcctcctc ccagttctcc tctggatcgc agncatccan agatgtgacc 180
tcttccagcc gccaaatccg caccaaggtc atggatgtgc acgatggcaa ggtgggtgtc 240
cacccacgaa caggtccttc gcaccaagaa ctgagg 276

<210> 81
<211> 647
<212> DNA
<213> Homo sapien

<400> 81
gtcctgcctt tcatcttttc tttaaaaaaa ataaatgttt acaaaacatt tccctcagat 60
tttaaaattc atggaagtaa taaacagtaa taaaatatgg atactatgaa aactgacaca 120
cagaaaaaca taaccataaa atattgttcc aggatacaga tattaattaa gagtgacttc 180
gttagcaaca cgtagacatt catacatatc cggtggaaga ctggtttctg agatgcgatt 240
gccatccaaa cgcaaatgct tgatcttgga gtaggrtaat ggccccagga tcttgcagaa 300
gctctttatg tcaaacttct caagttgatt gacctccagg taatagtttt caaggttttc 360
attgacagtt ggtatgtttt taagcttgtt ataggacaga tccagctcaa ccagggatga 420
cacattgaaa gaatttccag gtattccact atcagccagt tcgttgtgag ataaacgcag 480
atactgcaat gcattaaaac gcttgaaata ctcatcaggg atgttgctga tcttattgtt 540
gtctaagtag agagttagaa gagagacagg gagaccagaa ggcagtctgg ctatctgatt 600
gaagctcaag tcaaggtatt cgagtgattt aagaccttta aaagcag 647

<210> 82
<211> 878
<212> DNA
<213> Homo sapien

<400> 82
ccttctttcc ccactcaatt cttcctgccc tgttattaat taagatatct tcagcttgta 60
gtcagacaca atcagaatya cagaaaaatc ctgcctaagg caaagaaata taagacaaga 120
ctatgatatc aatgaatgtg ggttaagtaa tagatttcca gctaaattgg tctaaaaaag 180
aatattaagt gtggacagac ctatttcaaa ggagcttaat tgatctcact tgttttagtt 240
ctgatccagg gagatcaccc ctctaattat ttctgaactt ggttaataaa agtttataag 300
atttttatga agcagccact gtatgatatt ttaagcaaat atgttattta aaatattgat 360
ccttcccttg gaccaccttc atgttagttg ggtattataa ataagagata caaccatgaa 420
tatattatgt ttatacaaaa tcaatctgaa cacaattcat aaagatttct cttttatacc 480
ttcctcactg gccccctcca cctgcccata gtcaccaaat tctgttttaa atcaatgacc 540
taagatcaac aatgaagtat tttataaatg tatttatgct gctagactgt gggtcaaatg 600
tttccatttt caaattattt agaattctta tgagtttaaa atttgtaaat ttctaaatcc 660
aatcatgtaa aatgaaactg ttgctccatt ggagtagtct cccacctaaa tatcaagatg 720
gctatatgct aaaaagagaa aatatggtca agtctaaaat ggctaattgt cctatgatgc 780
tattatcata gactaatgac atttatcttc aaaacaccaa attgtcttta gaaaaattaa 840
tgtgattaca ggtagagaac ctcggccgcg accacgct 878

<210> 83
<211> 645
<212> DNA
<213> Homo sapien

<400> 83
acaaacattt tacaaaaaag aacattacca atatcagtgg cagtaagggc aagctgaaga 60
ataaatagac tgagtttccg ggcaatgtct gtcctcaaag acatccaaac tgcgttcagg 120
cagctgaaac aggcttcttt cccagtgaca agcatatgtg gtcagtaata caaacgatgg 180
taaatgaggc tactacatag gcccagttaa caaactcctc ttctcctcgg gtaggccatg 240
atacaagtgg aactcatcaa ataatttaaa cccaaggcga taacaacgct atttcccatc 300
taaactcatt taagccttca caatgtcgca atggattcag ttacttgcaa acgatcccgg 360
gttgtcatac agatacttgt ttttacacat aacgctgtgc catcccttcc ttcactgccc 420
cagtcaggtt tcctgttgtt ggaccgaaag gggatacatt ttagaaatgc ttccctcaag 480
acagaagtga gaaagaaagg agaccctgag gccaggatct attaaacctg gtgtgtgcgc 540
aaaagggagg gggaaggcag gaatttgaaa ggataaacgt ctcctttgcg ccgaggaatc 600

aggaagcgtg actcacttgg gtctgggacg ataccgaaat ccggt 645

<210> 84
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 84
tctgatgtca atcacaactt gaaggatgcc aatgatgtac caatccaatg tgaaatctct 60
cctcttatct cctatgctgg agaaggatta gaaggttatg tggcagataa agaattccat 120
gcacctctaa tcatcgatga gaatggagtt catgggctgg tgaaaaatgg tatttgaacc 180
agataccaag ttttgtttgc cacgatagga atagctttta tttttgatag accaactgtg 240
aacctacaag acgtcttgga caactgaagn ttaaatatcc acangggttt attttgcttg 300
g 301

<210> 85
<211> 296
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(296)
<223> n = A,T,C or G

<400> 85
agcgtgggtc gcggcncgan gtagagaacc gactgaaacg tttgagatga agaaagttct 60
cctcctgatc acagccatct tggcagtggc tgttggtttc ccagtctctc aagaccagga 120
acgagaaaaa agaagtatca gtgacagcga tgaattagct tcagggtttt ttgtgttccc 180
ttacccatat ccatttcgcc cacttccacc aattccattt ccaagatttc catggtttan 240
acgtaatttt cctattccaa tacctgaatc tgcccctaca actccccttc ctagcg 296

<210> 86
<211> 806
<212> DNA
<213> Homo sapien

<400> 86
tctacgatgg ccatttgctc attgtctttc ctctgtgtgt agtgagtgac cctggcagtg 60
tttgcctgct cagagtggcc cctcagaaca acagggctgg ccttggaaaa accccaaaac 120
aggactgtgg tgacaactct ggtcaggtgt gatttgacat gagggccgga ggcggttgct 180
gacggcagga ctggagaggc tgcgtgcccg gcactggcag cgaggctcgt gtgtccccca 240
ggcagatctg ggcactttcc caacccaggt ttatgccgtc tccagggaag cctcggtgcc 300
agagtggtgg gcagatctga ccatccccac agaccagaaa caaggaattt ctgggattac 360
ccagtccccc ttcaacccag ttgatgtaac cacctcattt tttacaaata cagaatctat 420
tctactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcatgc 480
tccgggcccc acgtggctcc tgtgctctag atcatggtga ctcccccgcc ctgtggttgg 540
aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg 600
ccctttaatg ggattgaaag cactttacc acatggagaa atatattttt aatttgtgat 660
gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc 720
taatgaaagc tgatgaattt tcttttctgt ccaaacaagt aaaataaaaa taaaagtcta 780
tttagatgtt gaaaaaaaaa aaaaaa 806

<210> 87
<211> 620
<212> DNA
<213> Homo sapien

<400> 87
ttttgcatc agatctgaaa tgtctgagag taatagtttc tgttgaattt ttttttgttc 60
atttttctgc acagtccatt ctgtttttat tactatctag gcttgaaata tatagtttga 120
aattatgaca tccttcctct ttgttatttt cctcatgatt gctttggcta ttcaaagttt 180
attttagttt catgtaaatt tttgaattgt attttccatt attgtgaaaa tagtaccact 240
gcaattttaa taggaagttt attgaatcta tagattactt tggataatat ggcacttcaa 300
taatattcat gttttcaatt catagacaaa atattttaaa atttatttgt atcttttcta 360
atttttcctt tttttattgt aaagatttac ctccttggtt aatattttcc tcagaaattt 420
attatttaag gtatagtcaa taaaattttc ttcctctatt ttgtcagata gtttaagtgt 480
atgaaaccat agatatactt gtatgttaat tttatatttt gctaatttac tgagtgtatt 540
tattagttta gagaggtttt aatgtactgt ttatggtttt ttaaatataa gattacttat 600
tttttaaaaa aaaaaaaaaa 620

<210> 88
<211> 308
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(308)
<223> n = A,T,C or G

<400> 88
tagctgtgnt cagcaggccg aggtttttt ttttttgag atggagtctc gccctgtcac 60
ccaggctgga gtgcagtggc ctgatctcag ctcactgcaa gctccacctc ctggattcac 120
gctattctcc tgcctcagcc tcccaagtag ctgggactac aggcgcccgc caccacgccc 180
agctaattnt ttgnattttt agtacnagat gcggtttcat cgtgttagcc agcatggnct 240
cgatctcctg acctcgtgaa ctgcccgcct cggcctccca aagacctgcc cgggcnggcc 300
gctcgaaa 308

<210> 89
<211> 492
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

<400> 89
agcggccgcc cgggcaggtc tgttaagtaa catacatatc accttaataa aaatcaagat 60
gaaatgtttt agaaactatt ttatcaaaag tggctctgat acaaagactt gtacatgatt 120
gttcacagca gcactattaa tgccaaaaag tagacaaaac ctaaatgtcc attaactgat 180
aagcaaaatg tggtatatcc atacaatgga atattatgta gcccacaaca tggcatggag 240
tactacaaca tggatgagcc tcaaaaacgt tatgctaaat gaaaaaagtc agatatagga 300
aaccacatgt catatgatcc catttatatg aaatagccag aaaaggcaag tcatagaaac 360
aagatagatc ggaaaatggg ttggaggact acaaatggca ccagggatct ttgaagttga 420
tggaaatggt ctaaaatcag actgtggntg tggttgaaca agtctgtaaa tttaccaaaa 480
tgcgttaata ca 492

<210> 90
<211> 390
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(390)
<223> n = A,T,C or G

<400> 90
tcgagcggcc gcccgggcag gtacaagctt ttttttttt ttttttttt ttttctaaca 60
gttctctgtt ttattgcaat acagcaaagt ctggttaata ttaagngata tcaacataaa 120
gtattggtga ggagtctttt gtgacatttt ttaccatccc accttaaata tttctgtgca 180
aaanaatcca catcattgtt tggtancana ggatctctta aaaagttccc taanacactg 240
agggcataaa accaaacaaa ataaaataag gagtgatagg ctaaagcagt atcttcccct 300
ccatccacat ttgncaagca ttatattcta accaaaaaat gatcacacca ggccatgcaa 360
aactgtccaa tattaccgag aaaaaaccct 390

<210> 91
<211> 192
<212> DNA
<213> Homo sapien

<400> 91
agcgtggtcg cggccgaggt ctgtcaatta atgctagtcc tcaggattta aaaaataatc 60
ttaactcaaa gtccaatgca aaaacattaa gttggtaatt actcttgatc ttgaattact 120
tccgttacga aagtccttca cattttcaa actaagctac tatatttaag gcctgcccgg 180
gcggccgctc ga 192

<210> 92
<211> 570
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(570)
<223> n = A,T,C or G

<400> 92
agcgtggtcg cggccgaggt ctgacaacta acaaagaagc aaaaactggc atcttggaca 60
tcctagtatt acacttgcaa gcaattagaa cacaaggagg gccaaggaaa aagtttagct 120
ttgaatcact tccaaatcta ctgattttga ggttccgcag tagttctaac aaaacttttc 180
agacaatgtt aactttcgat taagaaagaa aaaaacccca aacatcttca ggaattccat 240
gccaggttca gtctcttcca gtgagcccgc ttgctaaaag tccacgtgca ccattaatta 300
gctgggctgg cagcaccatg taaaaagaag cctattcacc accaaccaca cagactagac 360
atgtaaagta ggatcaagta atggatgaca accatggtcg tggaatatgg tcaatgagag 420
tcagaaaagt acaggcacca gtacaagcag cagataacag aattgacggg ccaaaggata 480
aaaataggct tatttaaata ggatgctaca gaacacatnc acttctaatt ggaagctgct 540
ttacactggg tggcattgna ccatatgcat 570

<210> 93
<211> 446
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(446)
<223> n = A,T,C or G

<400> 93
tcgagcggcc gcccgggcag gtccaggttt ttatttagtt gtgtaatctt ggacaagtta 60
cctaactttt ttgagtctga atatatttaa tctgcaaaat gagaatcatg ataatacgtc 120
ataggcttaa ttaggaggat taaatgaaat aatttatagg tggtgccatg gttacataca 180
agtattagta gttaattctt ttcctttgtt tacttttata gtataggttg gatgaaggtt 240
ccagtatagg caaaaatact acttgggggt aaagtagagt gtgatacttt atttgaaatg 300
ttccctgaat ctgatcttta ctttttgnta ctgctgcact acccaaatcc aaattttcat 360
cccaacattc ttggatttgt gggacagcng tagcagcttt tccaatataa tctatactac 420
atcttttctt actttggtgc ttttg 446

<210> 94
<211> 409
<212> DNA
<213> Homo sapien

<400> 94
cgagcggccg cccgggcagg tccatcagct cttctgctta gaatacgagg cagacagtgg 60
agaggtcaca tcagttatcg tctatcaggg tgatgaccca agaaaggtga gtgagaaggt 120
gtcggcacac acgcctctgg atccacccat gcgagaagcc ctcaagttgc gtatccagga 180
ggagattgca aagcgccaga gccaacactg accatgttga aggcgttctc tccaggctgg 240
attcactgca ctcggaagaa ttctgcccag ggaatttagt gtgggggtac caggaccagt 300
ttgtcttgat cttgagaccc ccagagctgc tgcatccata gggtgttgca ggactacacc 360
tggcctgcct tgcagtcatt ctttcttata tgttgaccca tttgcccaa 409

<210> 95
<211> 490
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(490)
<223> n = A,T,C or G

<400> 95
tcgagcggcc gcccgggcag gtcctacttg tttgcagctt ccacacactg cacctaccta 60
ctacctctct tccatgctta actgggttta gaaaggtgag ctatgcgtag aagaactact 120
tgggatattc aagtgctgta tttgaacgat aagcctatag ataacagtct gaagctgcaa 180
gggagacttt gttagtacac tactataaac aggtaaacta cctgtttgta cttgatatag 240
tgcatatgaa atgactgatt taatacaaaa ctacagaaca tgcaaaattt tttctgagat 300
gttaagtatt acttcagtgg agaacaaaac ttacttaacc tttcgctaat gcatgtagta 360
ccagaaagca aacatggttt tagcttcctt tactcaaaat atgaacatta agtggttgtg 420
aattttgtct gccaagtggt tcagaaaata cattataaat aacctaagtt aaaaaaaaga 480
aactgngaac 490

<210> 96
<211> 223
<212> DNA
<213> Homo sapien

<400> 96
agcgtggtcg cggccgaggt ctggaagccc accctaggac ttgaatggca ccttgtcctt 60
tctctgccag taatgcaatc caacacaata tgctacaggg aaaacagaat ttccacggtg 120
ccgccctctg gtacaaggga aacagcacgc aaagcaaaag gccacagagg gctccctgag 180
aatccagtac aactaagcga ggacctgccc gggcggccgc tcg 223

<210> 97
<211> 527
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(527)
<223> n = A,T,C or G

<400> 97
tcgagcggcc gcccgggcag gtctgtgcag gagacactga agtgggtagt gtccataatc 60
tttttagcct gttgctgaaa ttccagttgt actccttcaa accaaaatgc ttacaggatc 120
atgggaaagc ctcggttgca gaaatcaaga caggcaagtg ggaagataac tcggctttga 180
ggttaaacag atctgggttc aaagcatagt ttcactctct gtcttgtgaa gtgtcctggg 240

tgaagtcatt tcctctcttg aatttcagag aggatgaaaa tataaaaagt ataataacta 300
tcttcataat ctttgtgagg attaaagaag acgaagtgtg tgaaaagcta agcacagagc 360
aggcattcta caataagtag ttattatttt tggaaccatc ccgnccctag ccccagccca 420
attaccttct cttagnctct tcatatcgaa ngccgtaatc ttgaccttct cttgcnactg 480
gattggtgct ggttgatgcc caaacttccc gagatgctgt ctgggaa 527

<210> 98
<211> 514
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(514)
<223> n = A,T,C or G

<400> 98
tcgagcggcc gcccgggcag gtctggctcc catggccctt ggggtggcct gactctgtca 60
ctattcctaa aaccttctag gacatctgct ccaggaagaa ctttcaacac caaaattcat 120
ctcaatttta cagatgggaa aagtgattct gagaccagac cagggtcagg ccaaggtcat 180
ccagcatcag tggctgggct gagactgggc ccagggaacc ctgtctgctc ctcttttcc 240
cagagctgtg agttctctag ccaaggctgc actcttgagg gagagccagg aagcatagct 300
gaggccatga caacctcact cttcacctga aaatttaacc cgtggcagag gatccaggca 360
catataggct tcggagccaa acaggacctc ggccgcgacc acgctaagcc gaattccagc 420
acactggcgg ccgttactag tggatcccga gcttnggtac caagcttggc gtaatcatgg 480
gcatagctgg ttcctggggt gaaaatggta tccg 514

<210> 99
<211> 530
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(530)
<223> n = A,T,C or G

<400> 99
tcgagcggcc gcccgggcag gtctgaagaa acaggtataa atttggcagc cagtaatttt 60
gacagggaag ttacagcttg catgacttta aatatgtaaa tttgaaaata ctgaatttcg 120
agtaatcatt gtgctttgtg ttgatctgaa aaatataaca ctggctgtcg aagaagcatg 180
ttcaaaaata tttaattcac ttcaaaatgt catacaaatt atggtggttt ctatgcaccc 240
ctaaagcttc aagtcattta gctcaggtac atactaaagt aatatattaa ttcttccagt 300
acagtggtgt ttcataccat tgacatttgc ataccctaga ataatttaag aaagacatgt 360
gtaatattca caatgttcag aaaagcaagc aaaaggtcaa ggaacctgct ttggttcttc 420
tggagatggn ctcatatcag cttcataaac attcattcta caaaatagta agctaaccat 480
ttgaacccca atttccagat taagcatatt ttctcataaa tnatgaagcc 530

<210> 100
<211> 529
<212> DNA
<213> Homo sapien

<400> 100
agcgtggtcg cggccgaggt ccaggcacgg tggcttatgt gtgtaatccc agcacttggg 60
gaggctgagg gaggtggatc acttgagtcc aggagtttga gaccagtctg ggcaacatgg 120
cgaaacttca tcactaccaa agaagaaaaa aattagccag gtgtggtggt gtatgcctgt 180
agtcccagat actctggtgg ctgaggtgag aggatagctt gagcccagga aattgaggct 240
gcagtgaact atgattgcac tactgtgctc cagcttgggc aacagagtga gatcttgtct 300
ccaaaagtcc ttgaaggatt ttaggaagtt gttaaaagtc ttgaaacgat gtttgggggc 360
atgttagggt tcttgaatgt ttaattcctc taataactgc ttattcaaga gaagcatttc 420
tgactgggtg cggggcagtg gcttcatgcc ccataatccc agtactttgg gaggctgaag 480

caggaacatt gcttgagccc aggacttcaa gaacagcctg ggtaacata 529

<210> 101
<211> 277
<212> DNA
<213> Homo sapien

<400> 101
tcgagcggcc gcccgggcag gtcgcaggaa gaggatggaa actgaggagt ccaggaagaa 60
gagggaacga gatcttgagc tggaaatggg agatgattat attttggatc ttcagaagta 120
ctgggattta atgaatttgt ctgaaaaaca tgataagata ccagaaatct gggaaggcca 180
taatatagct gattatattg atccagccat catgaagaaa ttggaagaat tagaaaaaga 240
agaagagctg agaacagacc tcggccgcga ccacgct 277

<210> 102
<211> 490
<212> DNA
<213> Homo sapien

<400> 102
gcgtggtcgc ggccgaggtc tgacggcttt gctgtcccag agccgcctaa acgcaagaaa 60
agtcgatggg acagttagag gggatgtgct aaagcgtgaa atcagttgtc cttaattttt 120
agaaagattt tggtaactag gtgtctcagg gctgggttgg ggtccaaagt gtaaggaccc 180
cctgccctta gtggagagct ggagcttgga gacattaccc cttcatcaga aggaattttc 240
ggatgttttc ttgggaagct gttttggtcc ttggaagcag tgagagctgg gaagcttctt 300
ttggctctag gtgagttgtc atgtgggtaa gttgaggtta tcttgggata aagggtcttc 360
tagggcacaa aactcactct aggtttatat tgtatgtagc ttatattttt tactaaggtg 420
tcaccttata agcatctata aattgacttc tttttcttag ttgtatgacc tgccccgggc 480
ggccgctcga 490

<210> 103
<211> 490
<212> DNA
<213> Homo sapien

<400> 103
gagcggccgc ccgggcaggt ccaaaccagc ttgctcataa gtcattaacc aaatccatta 60
taggtaattt gttcagttca atgtttacaa ttcttatgga aaaaattagc aacacacaca 120
tttaaaacgt gtgcatttac ctttgcgtga gtgcttaaaa tacatatttc tatttcaaga 180
tgacatttaa aaattattct aatatatcag cagcaaaaat ataatttgca attacaaaaa 240
actaaactag aatccttaag ttattctcat gtttacagtt gtgattcttt aataaatact 300
attatgcagc tctattgttt aagctttctg gatttggttt aaacacatgc atatatattg 360
tcaattgtgg gaagctttac aagttatatt ccatgcactt tttggacaga gttctaacag 420
agccagccag tccacaaaac aggcaagaca aaagttgaat taactggggc aaaataggac 480
tcttatgcaa 490

<210> 104
<211> 489
<212> DNA
<213> Homo sapien

<400> 104
cgtggtcgcg gccgaggtcc aggctggtct cgaactcctg accttgtgat ctgcccgcct 60
cggcctccca aagtgttggg attacaggca tgagccactg cgcccgaccg agttgaacat 120
ttaatgtcag actaggccag agtttctcaa tctttttatt ctcacttccc aaaggagccg 180
ttggagattt tcccctcaat ctctctcctt catgaaattt cataccacaa atatagtatg 240
ttttatttat gtactgtgac cctttgaagg atcacaaacc aatataatag tttttctttt 300
taacccgtca aggaccaagt ttttgccccc gttggaaatg cataaactgg actgatgaat 360
tggtatagat ggcttttatc atgaggatca gaaaaacttg aaattccttg gctacgacac 420
tccatattta tcaccgtata gggaggacct tggtatgggg aagtagaaac acttctacac 480
tttacagca 489

<210> 105
<211> 479
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(479)
<223> n = A,T,C or G

<400> 105
gcgtggtcgc ggccgaggtc tgactggctt cagccccaga agttgagctg gcctttagac 60
aaaataattg cacctccctc tgctgcttat tcccttccgt ttttcatttg agtgtgaaca 120
gttagataaa atctgtggct gnctcttcca ccttgctcta gtttccattg ctgtgagcag 180
gccctcctat gccccgcatt tagctacaat gctgtggact cacttgattc tttttctccg 240
agctttgtct agaaatatgt gaaggtgagg ttaagtgctt ctctgtgtag atccacttag 300
ccctgtctgc tgtctcgatg ggcgttgctt cgtctctcct ctcttccatc ctttccattt 360
gcttctcacc accttctggc ttcttttctt aatgcaataa aggcagtttc taacaaagaa 420
agaatgtggg ctttggagtt agacagacct ggntttaaat tctgcttctg gctctccaa 479

<210> 106
<211> 511
<212> DNA
<213> Homo sapien

<400> 106
tcgcggccga ggtccaaaac gtggattcca atgacctgcc ttgagcccgc ggttgccagg 60
agttggacct gcagtagtat gggaagctca cggcctaaat accgactgcc ctctgacccc 120
accgtccagc gattctagaa catttctagt aggaaagaca tagcaaggga ttttcatgat 180
tgggaaatac tgggagacaa gctgaagatt tgttaagggc tatgcttctg tcatctttta 240
ggtatttaag gctactcctt tagctagcta ctttgagctg tttaaagtga ctatctccct 300
acacagagtt acacaatgag catctctgaa agagaatatt accctggatt tccaaagatg 360
tactctaaca ggatgaccag gcaaaaggtg acccggggga ggagtctgtt ataacactcg 420
gacccacatg ttctcaaggc acttcagaac tttgggaaat cattttgtac cggatcctca 480
gaaagcattt atggaaatac acatccttta g 511

<210> 107
<211> 451
<212> DNA
<213> Homo sapien

<400> 107
ggccgcccgg gcaggtccag aatatcaaat caaaaggtca caaatgttca cttcctcctc 60
caccctctta catattggat cttcaattgc aatagggagt gtaagatggg cattttagag 120
acgtagttgc atcagcagaa gcaaacccat cttatacaaa tgggttttgg ggataggaaa 180
aggctgctaa aaattcacaa gtcaccattc cccagaagca atgaatagcc gtagaagacc 240
aaggaagatc aacaagtttc caaagtgcta aagccagaga tttggccctt ccaaaatacc 300
accaggacgc ctggacccgt gggctctccg catgtcacca ctgactgcca ggatgctgct 360
gcacctccct tccttgagac acaacagaga gacagtgaag tcacccaaga ctgggatcat 420
cagaggctcc tcatgcttgc tacagagaag c 451

<210> 108
<211> 461
<212> DNA
<213> Homo sapien

<400> 108
ccgcccgggc aggtcctgaa aacattcaga ctaatcaaaa tggtactact gtaacttctt 60
ataatacata atataaaagt ttttgaaaga tatagacaca attaacccct aaacaacaca 120
ctatctgatt ctcaaaagca atggctattt aacaagatgt aaaaggacaa taacatatca 180
aagaactttc acacacctaa agatagcatt tagcagcaag ttagtcagac aaaacaaaca 240
caaatatttt cacatttcct atgtttgttt ttaactttac ttcataaagc cactgataat 300

tgaggtttct ttcaagtata agatttctaa aattaaaaac tgtttttgac atatttttat 360
aaagaaataa aaagcaaaac gcaatccaac tatttatatg agtccctctt ctccaacagc 420
tttagatggt tttctgagta ctttttttaca cagaatattt t 461

<210> 109
<211> 441
<212> DNA
<213> Homo sapien

<400> 109
ggccgcccgg gcaggtctga ttataagaga aagaaatcca gtgacacgag ggcaggcagg 60
ccccgctctg ctctgatcga gaaaagcttc ctgatgtcag ggagatggaa ctgccaccat 120
cagaaccatg gcactttggg tgaaggtgtg tcagcgacca agggggcagg aaatgggcag 180
tgactaaggg ggcaggaaac aggcaggcac atggcaaggt tctcccagcc catcagccca 240
gtgatggcct cgattttgaa gctgcactac tgtctgaaaa gcacaattac tggtgactct 300
taacaaactt cagcatactg gggaaggaga ctgtcaagta actgaattgg aaagatgaaa 360
aagaaccatc tctaaaagtt gatgcttgtc agaagaataa cctcctttgt gcaagtcttg 420
caacatcttc attcaaccac a 441

<210> 110
<211> 451
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(451)
<223> n = A,T,C or G

<400> 110
ggtcgcggcc gaggtctggg gaaggggtga gaatccctgg gccttgccca gtcctgagct 60
ctgggtgtct gcagggaagc acagtggtga gttagtgtta aagaaagcat ccagagaggt 120
aagaggggct tgggtagcac cctttgcctc tgtcacttcc gcaaaaactt cttgttgagg 180
aggaagatga gaaggttgac attgactttg gccttgttga agagtttcat gacagccaca 240
ccctcatact ggagctgcan gagatcctga tagtgaagct tgaaatcgct ccatgtccac 300
acccaggaac ttggcattta cttcaaactt tcctgcctca tctcccggcg tgatgtcaaa 360
natgacgttt cttgaagtga gaggcgggaa agatcttcaa tttccaccaa agacaccctt 420
tttccaggaa gcttgagcaa caagtgtaat g 451

<210> 111
<211> 407
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(407)
<223> n = A,T,C or G

<400> 111
ggccgacgtt cgacctgact tctttngagc agntgncact acccgtcttg aggaatgccg 60
actgcagaca gtggcccang gcaaagagtg tgcgtcatcg atganattgg naagatggag 120
ctcttcagtc agnttttcat tcaagctgnt cgtcagacgc tgtctacccc agggactata 180
atcctnggca caatcccagt tcctanagga aagccactgn ctcttgtaga agaaatcana 240
cacanaaagg atgtgaacng tgtttaatgt caccaaggga aaacatgaaa ccaccttctg 300
ccagatatcg ggacgttgcg tgcagatcaa gcacgnaagt gaagacgcgt gcattccttg 360
ccttccgtga acgantgccc agntcaagaa gancctgatg gaaccct 407

<210> 112
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 112
tcgcggccga ggtcggccga ggtctgacat ctgttgtctg tgataaccac ttctgtattg 60
cgtcttaacc acttctgtat tgtgtggttt taactgccta aggcggcaat gggcagtggg 120
ccccttccc ttaggatggg tatcaattca acaatattta taaggcattt actgtgtgct 180
aagcatttgg aagacccagg ctacaaaata agacatagtt cctgccctcc aggccagcag 240
agggaggcac aaatacccag gaatctctga tgggtgtgaa gtgcggtcgt gggccacaga 300
aaatgaccgt catggagacc ctgctaaagg tcggaccctg agcccaaagg ggtattcaga 360
agnggagatg attttggccc cactcataga tgggtggcaa a 401

<210> 113
<211> 451
<212> DNA
<213> Homo sapien

<400> 113
gtcgcggccg aggtccatat taaaaagtcc atcataaaca aagactcctc ctcatggtat 60
gaatatgctc catatgccca taatggtgca taacggactt agaaattcca atgagtctta 120
gggttgaaat ttccaatgac ctgagcaagg cagctcccta tagcttctgg ataacatttt 180
acacccagag ttcaggctta aacagaccta tcaacacaat tattttcgga ttgtctgtct 240
agaaaacggc aatgctcaaa ggaatataaa taagggtggg gggacatatg cttccagcct 300
ggcctttctc catgtggtaa aaaacaatgg aatggctgtg ttaatttttt tttaatcttt 360
tctgaccttt actatgtttg gtaatggaaa taagtcaggg aaaacaaaat gaacaggtct 420
catcacttaa ttaatactgg gttttcttct t 451

<210> 114
<211> 441
<212> DNA
<213> Homo sapien

<400> 114
ggccgcccgg gcaggtccat cctgtcagag atgggagaag tcacagacgg aatgatggat 60
acaaagatgg ttcactttct tacacactat gctgacaaga ttgaatctgt tcatttttca 120
gaccagttct ctggtccaaa aattatgcaa gaggaaggtc agcctttaaa gctacctgac 180
actaagagga cactgttgtt tacatttaat gtgcctggct caggtaacac ttacccaaag 240
gatatggagg cactgctacc cctgatgaac atggtgattt attctattga taaagccaaa 300
aagttccgac tcaacagaga aggcaaacaa aaagcagata agaaccgtgc ccgagtagaa 360
gagaacttct tgaaacttga cacatgtgca aagacaggaa gcagcacagt ctcggcggga 420
ggaagaaaaa aagaacagag a 441

<210> 115
<211> 431
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(431)
<223> n = A,T,C or G

<400> 115
gccgcccggg caggtccatt ggcggtgaca aaaggaaaag aagcaaagag actcagtcca 60
taatgctgat tagttagaag aaagggctag gattgagaaa gtaccaggaa cttttaatta 120
tttaaaagag aatgctgact gttaatgttt taaatcttac tgttcaaatg tactaatatg 180
aatttttacc ctttgtgcat gaatattcta aacaactaga agacctccac aatttagcag 240
ttatgaaagt taaacttttt attataaaaa ttctaaacct tactgctcct ttaccaggaa 300
catgacacac tatttancat cagttgcata cctcgccaat agtataattc aactgtcttg 360

cccgaacaat catctccatc tggaagacgt aagcctttag aaacacattt ttctattaat 420
ttctctagaa c 431

<210> 116
<211> 421
<212> DNA
<213> Homo sapien

<400> 116
gtcgcggccg aggtccagaa atgaagaaga agtttgcaga tgtatttgca aagaagacga 60
aggcagagtg gtgtcaaatc tttgacggca cagatgcctg tgtgactccg gttctgactt 120
ttgaggaggt tgttcatcat gatcacaaca aggaaccggg gctcgtttat caccagtgag 180
gagcaggacg tgagcccccg ccctgcacct ctgctgttaa acaccccagc catcccttct 240
ttcaaaaggg atcctttcat aggagaacac actgaggaga tacttgaaga atttggattc 300
agcccgcgaa gagatttatc aagcttaact cagataaaat cattgaaagt aataaggtaa 360
aagctaagtc tctaacttcc aggcccacgg ctcaagtgaa tttcgaatac tgcatttaca 420
g 421

<210> 117
<211> 489
<212> DNA
<213> Homo sapien

<400> 117
agcgtggtcg cggccgaggt aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 60
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 120
ctactacgtt gacactgctg tgcgccacgt gttgctcaga cagggtgtgc tgggcatcaa 180
ggtgaagatc atgctgccct gggacccaac tggtaagatt ggccctaaga agcccctgcc 240
tgaccacgtg agcattgtgg aacccaaaga tgagatactg cccaccaccc ccatctcaga 300
acagaagggt gggaagccag agccgcctgc catgccccag ccagtcccca cagcataaca 360
gggtctcctt ggcagacctg cccgggcggc cgctcgaaag cccgaattcc agcacactgg 420
cggccgttac tagtggatcc cagctcggta ccaagcttgg cgtaatcatg gtcatagctg 480
gtttcctgt 489

<210> 118
<211> 489
<212> DNA
<213> Homo sapien

<400> 118
tcgagcggcc gcccgggcag gtattgaata cagcaaaatt ctatatacaa agtgacctgg 60
acctgctgct tcaaaacatg atcctttctt actaatatct tgatagtcgg tccatagagc 120
attagaaagc aattgactct taaataaaca gaaaagtgcc taatgcacat taaatgaatg 180
gcctaactac tggaacttta gtagttctat aaggtgatta acataggtag gatccagttc 240
ctatgacagg ctgctgaaga acagatatga gcatcaagag gccattttgt gcactgccac 300
cgtgatgcca tcgtgtttct ggatcataat gttcccatta tctgattcta gacacaccac 360
aggaatatca gtggggtcag aggttagctt agctgcttgc tgggctagaa cagatatcac 420
tccagcatgc tcatctgaca gggtcccgcg gcaacccaga ttaagtcctt gtgaatctgt 480
gcacaggga 489

<210> 119
<211> 181
<212> DNA
<213> Homo sapien

<400> 119
taggttccag agacttttgg cccaggagga atatttactt ttagctctgg acatcattac 60
aaaaaggaat atttcccaaa cctcttcaga ccgagaatac atgggtaaaa ttattaaata 120
gttgtataat aaaaataatt ttttccttaa aaaaaaaaaa aacctcggcc gcgaccacgc 180
t 181

<210> 120

<211> 489
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(489)
<223> n = A,T,C or G

<400> 120
gcgtggtcgc ggccgaggtc catttaaaac aaagaaaaat actaaagcca ctagtaaaca 60
tctgatgtgc aaaatacaac atcctctagt tggctttatg ccattattac ataagctcca 120
aatagctcat cttaaattaa aaagaaaaag tggctgtccc atctctgctg cataaatcag 180
atttttttt aaaggtttag agtactttaa ggaagggaag ttcaaaactg ccagtgaaat 240
tcacagagaa tacaaattta gcaatttaat ttcccaaagc tctttgaaga agcaagagag 300
tctctcttct taatgcagtg ttctcccaag aggaactgta attttgcttg gtacttatgc 360
tgggagatat gcaaaatgtg tttttcaatg tttgctagaa tataatggtt cctcttcagt 420
gnctggttca tcctggaact catgggttaa gaaggacttc ttggagccga actgcccggg 480
cgggccntt 489

<210> 121
<211> 531
<212> DNA
<213> Homo sapien

<400> 121
cgagcggccg cccgggcagg tggccagcgc tggtcccgca gacgccgaga tggaggaaat 60
atttgatgat gcgtcacctg gaaagcaaaa ggaaatccaa gaaccagatc ctacctatga 120
agaaaaaatg caaactgacc gggcaaatag attcgagtat ttattaaagc agacagaact 180
ttttgcacat ttcattcaac ctgctgctca gaagactcca acttcacctt tgaagatgaa 240
accagggcgc ccacgaataa aaaaagatga gaagcagaac ttactatccg ttggcgatta 300
ccgacaccgt agaacagagc aagaggagga tgaagagcta ttaacagaaa gctccaaagc 360
aaccaatgtt tgcactcgat ttgaagactc tccatcgtat gtaaaatggg gtaaactgag 420
agattatcag gtcccgagga ttaaactggc tcatttcttt gtatgagaat ggcatcaatg 480
gtatccttgc agatgaaatg ggcctaggaa agactcttca acaatttctc t 531

<210> 122
<211> 174
<212> DNA
<213> Homo sapien

<400> 122
tcgagcggcc gcccgggcag gtctgccaac agcagaggcg gggcctccgg catcttcaaa 60
gcacctctga gcaggctcca gccctctggc tgcgggaggg gtctggggtc tcctctgagc 120
tcggcagcaa agcagatgtt atttctctcc cgcgacctcg gccgcgacca cgct 174

<210> 123
<211> 531
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(531)
<223> n = A,T,C or G

<400> 123
agcgtggtcg cggccgaggt cctcaaccaa gagggttgat ggcctccagt caagaaactg 60
tggctcatgc cagcagagct ctctcctcgt ccagcaggcg ccatgcaagg gcaggctaaa 120
agacctccag tgcatcaaca tccatctagc anagagaaaa ggggcactga agcagctatg 180
tctgccaggg gctaggggct cccttgcaga cagcaatgct acaataaagg acacagaaat 240
gggggaggtg ggggaagccc tatttttata acaaagtcaa acagatctgt gccgttcatt 300

ccccccagaca cacaagtaga aaaaaaccaa tgcttgtggt ttctgccaag atggaatatt 360
cctccttcct aanttccaca catggccgtt tgcaatgctc gacagcattg cactgggctg 420
cttgtctctg tggtctgggc accagtagct tgggccccat atacacttct cagttcccac 480
anggcttatg gccnangggc angctccaat tttcaagcac cacgaaggaa g 531

<210> 124
<211> 416
<212> DNA
<213> Homo sapien

<400> 124
tcgagcggcc gcccgggcag gtccatctat actttctaga gcagtaaatc tcataaattc 60
acttaccaag cccaggaata atgactttta aagccttgaa tatcaactaa gacaaattat 120
gccaattctg atttctcaca tatacttaga ttacacaaag ataaagcttt agatgtgatc 180
attgtttaat gtagacttat ctttaaagtt tttaattaaa aactacagaa gggagtaaac 240
agcaagccaa atgatttaac caaatgattt aagagtaaaa ctcactcaga aagcattata 300
cgtaactaaa tatacatgag catgattata tacatacatg aaactgcaat tttatggcat 360
tctaagtaac tcatttaagt acatttttgg catttaaaca aagatcaaat caagct 416

<210> 125
<211> 199
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(199)
<223> n = A,T,C or G

<400> 125
agcgtggtcg cggccgaggt gctttttttt ttttttttt ttttttttt gctattctaa 60
aggggaaggc ccctttttat taaacttgta cattttactt tccttctttc anaatgctaa 120
taaaaaactt ttgtttatac ttaaaaaaac cataaatcan acaaacaaaa gaaacgattc 180
caacatcact tctgngatg 199

<210> 126
<211> 490
<212> DNA
<213> Homo sapien

<400> 126
cgtggtcgcg gccgaggtcc agttgctcta agtggattgg atatggttgg agtggcacag 60
actggatctg ggaaaacatt gtcttatttg cttcctgcca ttgtccacat caatcatcag 120
ccattcctag agagaggcga tgggcctatt tgtttggtgc tggcaccaac tcgggaactg 180
gcccaacagg tgcagcaagt agctgctgaa tattgtagag catgtcgctt gaagtctact 240
tgtatctacg gtggtgctcc taagggacca caaatacgtg atttggagag aggtgtggaa 300
atctgtattg caacacctgg aagactgatt gacttttag agtgtggaaa aaccaatctg 360
agaagaacaa cctaccttgt ccttgatgaa gcagatagaa tgcttgatat gggctttgaa 420
ccccaaataa ggaagattgt ggatcaaata agacctgata ggcaaactct aatgtggagt 480
gcgacttggc 490

<210> 127
<211> 490
<212> DNA
<213> Homo sapien

<400> 127
cgtggtcgcg gccgaggtcg gccgaggtct ggagatctga gaacgggcag actgcctcct 60
caagtgggtc cctgacccct gacccccgag cagcctaact gggaggcacc ccccagcagg 120
ggcacactga cacctcacac ggcagggtat tccaacagac ctgaagctga gggtcctgtc 180
tgttagaagg aaaactaaca agcagaaagg acagccacat caaaaaccca tctgtacatc 240
accatcatca aagaccaaaa gtaaataaaa ccacaaagat gggaaaaaaa cagaacagaa 300

aaactggaaa ctctaaaaag cagagcacct ctcctcttcc aaaggaacgc agttcctcac 360
cagcaatgga acaaagctgg atggagaatg actttgacga gctgagaaaa gaacgcttca 420
gacgatcaaa ttactctgag ctacgggagg acattcaaac caaaggcaaa gaagttgaaa 480
actttgaaaa 490

<210> 128
<211> 469
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(469)
<223> n = A,T,C or G

<400> 128
cgtggtcgcg gccgaggtgc ttttttttt ttttttttt ttttttttt tgctgattta 60
ttttttctnt ttattgttac atacaatgta taaacacata aaacanaaaa cagtagggat 120
cctctaggat ctctagggan acagtaaagt anaaagaggt ctcanaaaca tttttttaaa 180
gtacaagaca ttcagngctc ggcccaaagg cgtaaaaggt ttanagccag canatagctg 240
nactaaaggc tccgtctntn tccccanagc caggacaacc ccagggagct ntccattagc 300
agccagtcca cgcaggcagg atgctgcgga aaaagctcta tgctganaac attccccttg 360
atggaaagaa gggcaacaca aaaggggtaa ctaanagctc cttcctctcg tgagggcgac 420
aactgaggaa cagaaaagga gtgtcccatg tcacttttga ccccctccc 469

<210> 129
<211> 419
<212> DNA
<213> Homo sapien

<400> 129
gcgtggtcgc ggccgaggtc tgattttcat ttaaatattt cagagctata gcatttgcct 60
ccatgctcaa atccacacca ttggggctta agccgctcat gccaacatta gcaaatgaca 120
tgcagtttaa tccagagatc actgcttctg ggctgatgca tgccaacaca ctggcgtgat 180
ccacgttatg tgcatttttc ttcactttag tgggagaatc aatttttact ccaaggcttc 240
ttagttgctt aagagttgca ttaaggacac aatctttgtc caccagtctt gaatgatgtg 300
ttttttttctt tgtatggtaa acgttttggg ttctggtgca ttcatgactg ataattactg 360
ctttggtaga cggctgctca agtttccttg gaggaactat ttaataggtg ggttacttg 419

<210> 130
<211> 354
<212> DNA
<213> Homo sapien

<400> 130
agcgtggtcg cggccgaggt ccatctgagg agataaccac atcactaaca aagtgggagt 60
gaccccgcag agcacgctgt ggaattccat agttggtctc atccctggtc agtttccaca 120
tgatgatggt cttatctcga gaggcggaga ggatcatgtc cgggaactgc ggggtagtag 180
cgatctgggt tacccagccg ttgtggccct tgagggtgcc acgaagggtc atctgctcag 240
tcatggcggc ggcgagagcg tgtgtcgctg cagcgacgag gatggcactg gatggcttag 300
agaaactagc accacaacct ctcctgccgc acctgcccgg gcggcccgct cgaa 354

<210> 131
<211> 474
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(474)
<223> n = A,T,C or G

<400> 131
cgagcggccg cccgggcagg tctggcagca gcttcctctg gaataattga cagctttgtg 60
ctgcctgact aaaatttgaa atgacaaccg ctgaatgtaa aatgatgtac ctacaatgag 120
agagatttag gaatactatc tgtcaatcca tagatgtaga aacaaaacaa actacagaat 180
gaaaacaaac ttattttaaa ccaaagaaac aaatgtatcc aaaatatagt ccatgatata 240
tttgattact agtataacca cagttgaaaa cttaaaaaaa aaaattgaca ttttttgtaa 300
tgggtactaa tggatttata aaaggtttct gtttccaaag atgttattgg ggtccacata 360
ttccttgaag acttcagcat cccaaagccc gacatcagag atactttcct ttagccattg 420
nttcccgtaa cttgcccact ccatggtgat gtgacaggct tcccttcatt agca 474

<210> 132
<211> 474
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(474)
<223> n = A,T,C or G

<400> 132
ggccgaggtg gggaattcat gtggaggtca gagtggaagc aggtgtgaga gggtccagca 60
gaaggaaaca tggctgccaa agtgtttgag tccattggca agtttggcct ggccttagct 120
gttgcaggag gcgtggtgaa ctctgcctta tataatgtgg atgctgggca cagagctgtc 180
atctttgacc gattccgtgg agtgcaggac attgtggtag gggaagggac tcatttctc 240
atcccgtggg tacagaaacc aattatcttt gactgccgtt ctcgaccacg taatgtgcca 300
gtcatcactg gtagcaaaga tttacagaat gtcaacatca cactgcgcat cctcttccgg 360
cctgtcgcca gccagcttcc tcgcatcttc accagcatcg ganaggacta tgatgaaccg 420
tgtgctgccg tccatcacaa ctgagatcct caagtcagtg gtggctcgct ttga 474

<210> 133
<211> 387
<212> DNA
<213> Homo sapien

<400> 133
tgctcgagcg gccgccagtg tgatggatat ctgcagaatt cggcttagcg tggtcgcggc 60
cgaggtctgc gggcccctta gcctgccctg cttccaagcg acggccatcc cagtagggga 120
ctttcccaca ctgtgccttt acgatcagcg tgacagagta gaagctggag tgcctcacca 180
cacggcccgg aaacagcggg aagtaactgg aaagagcttt aggacagctt agatgccgag 240
tgggcgaatg ccagaccaat gatacccaga gctacctgcc gccaacttgt tgagatgtgt 300
gtttgactgt gagagagtgt gtgtttgtgt gtgtgttttg ccatgaactg tggccccagt 360
gtatagtgtt tcagtggggg agaactg 387

<210> 134
<211> 401
<212> DNA
<213> Homo sapien

<400> 134
ggccgcccgg gcaggtctga tgaagaacac gggtgtgatc cttgccaatg acgccaatgc 60
tgagcggctc aagagtgttg tgggcaactt gcatcggctg ggagtcacca acaccattat 120
cagccactat gatgggcgcc agttccccaa ggtggtgggg ggctttgacc gagtactgct 180
ggatgctccc tgcagtggca ctggggtcat ctccaaggat ccagccgtga agactaacaa 240
ggatgagaag gacatcctgc gcttgtgctc acctccagaa ggaagtttgct cctgagtgct 300
attgactctt gtcaatgcga ccttcaagac aggaggctac ctggtttact gcacctgttc 360
tatcacagtg agacctctgc catggcagaa caggggaagc t 401

<210> 135
<211> 451
<212> DNA
<213> Homo sapien

<400> 135
ggtcgcggcc gaggtctgtt cctgagaaca gcctgcattg gaatctacag agaggacaac 60
taatgtgagt gaggaagtga ctgtatgtgg actgtggaga aagtaagtca cgtgggccct 120
tgaggacctg gactgggtta ggaacagttg tactttcaga ggtgaggtgt cgagaaggga 180
aagtgaatgt ggtctggagt gtgtccttgg ccttggctcc acagggtgtg ctttcctctg 240
gggccgtcag ggagctcatc ccttgtgttc tgccagggtg gggtaccggg gtttgacact 300
gaggagggta acctgctggc tggagcggca gaacagtggc cttgatttgt cttttggaag 360
attttaaaaa ccaaaaagca taaacattct ggtccttcac aatgctttct ctgaagaaat 420
acttaacgga aggacttctc cattcaccat t 451

<210> 136
<211> 411
<212> DNA
<213> Homo sapien

<400> 136
ggccgcccgg gcaggtctga atcacgtaga atttgaagat caagatgatg aagccagagt 60
tcagtatgag ggttttcgac ctgggatgta tgtccgcgtt gagattgaaa atgttccctg 120
tgaatttgtg cagaactttg acccccttta ccccattatc ctgggtggct tgggcaacag 180
tgagggaaat gttggacatg tgcaggtggg tccctttgct gcgtatttgg tgcctgaggc 240
tctgtggatt tcccctccat caatcatctt accctctcat ccccctcaga tgcgtctgaa 300
gaaacatctc tggtataaga aaatcctcaa gtcccaagat ccaatcatat tttctgtagg 360
gtggaggaag tttcagacca tcctgctcta ttatatccga agaccacaat g 411

<210> 137
<211> 211
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(211)
<223> n = A,T,C or G

<400> 137
cggccgcccg ggcaggtcgg ttggtgcggc ctccattgtt cgtgttttaa ggcgccatga 60
ggggtgacag aggccgtggt cgtggtgggc gctttggttc cagaggaggc ccaggaggag 120
ggttcaggcc ctttgcacca catatcccat ttgacttcta tttgtgtgaa atggcctttc 180
cccggntcaa gccagcacct cgatgaaact t 211

<210> 138
<211> 471
<212> DNA
<213> Homo sapien

<400> 138
gccgcccggg caggtctggg ctggcgactg gcatccaggc cgtaactgca aatctatgct 60
aggcggggtc tcccttctgt gtgttcaagt gttctcgact tggattctta actattttaa 120
aaaatgcact gagtttgggt taaaaaccaa ccaccaaaat ggatttcaac acagctctaa 180
agccaagggc gtggccggct ctcccaacac agcgactcct ggaggccagg tgcccatggg 240
cctacatccc ctctcagcac tgaacagtga gttgattttt ctttttacaa taaaaaaagc 300
tgagtaatat tgcataggag taccaagaaa ctgcctcatt ggaaacaaaa actatttaca 360
ttaaataaaa agcctggccg caggctgcgt ctgccacatt tacagcacgg tgcgatgcac 420
acggtgacca aaccacggag gcaagcttct ggcactcaca ccacgacccg c 471

<210> 139
<211> 481
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

<400> 139
gtcgcggccg aggtctgttc tttagctcag atttaaacct gctgtctctt ctttatttgc 60
agaatgaatt cccagttcct gagcagttca agaccctatg gaacgggcag aagttggtca 120
ccacagtgac agaaattgct ggataagcga agtgccactg ggttctttgc cctcccttca 180
caccatggga taaatctgta tcaagacggt tcttttctag atttcctcta ccttttgct 240
cttaaaactg cttctctgct ctgagaagca cagctacctg ccttcactga aatatacctc 300
aggctgaaat ttggggtggg atagcaggtc agttgatctt ctgcaggaag gtgcagcttt 360
tccatatcag ctcaaccacg ccgncagtcc attcttaagg aactgccgac taggactgat 420
gatgcatttt agcttttgag cttttgggggg gtattctacc aaccaacagt ccatttggaa 480
a 481

<210> 140
<211> 421
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(421)
<223> n = A,T,C or G

<400> 140
gtcgcggccg aggtttccca tttaagaaaa atagatcttg agattctgat tcttttccaa 60
acagtcccct gctttcatgt acagcttttt ctttacctta cccaaaattc tggccttgaa 120
gcagttttcc tctatggctt tgcctttctg attttctcag aggctcgagt ctttaatata 180
accccaaatg aaagaaccaa ggggaggggt gggatggcac tttttttgt tggtcttgtt 240
ttgttttgtt ttttggttgg ttgggttccg ttatttttta agattagcca ttctctgctg 300
ctatttccct acataatgtc aatttttaac cataattttg acatgattga gatgtacttg 360
aggctttttt gntttaattg agaaaagact ttgcaatttt ttttttagga tgagcctctc 420
c 421

<210> 141
<211> 242
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(242)
<223> n = A,T,C or G

<400> 141
cgantngccc gcccgggcan gtctgtctaa ntttntcang gaccacgaac agaaactcgt 60
gcttcaccga anaacaatat cttaaacatc gaanaattta aatattatga aaaaaaacat 120
tgcaaaatat aaaataaata nnaaaaggaa aggaaacttt gaaccttatg taccgagcaa 180
atccaggtct agcaaacagt gctagtccta nattacttga tntacaacaa cacatgaata 240
ca 242

<210> 142
<211> 551
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(551)
<223> n = A,T,C or G

<400> 142
agcgtggtcg cggcncgang tccacagggc anatattctt ttagtgtctg gaattaaaat 60
gtttgaggtt tangtttgcc attgtctttc caaaaggcca aataattcan atgtaaccac 120
accaagtgca aacctgtgct ttctatttca cgtactgttg tccatacagt tctaaataca 180
tgtgcagggg attgtagcta atgcattaca cagtcgttca gtcttctctg cagacacact 240
aagtgatcat accaacgtgt tatacactca actagaanat aataagcttt aatctgaggg 300
caagtacagt cctgacaaaa gggcaagttt gcataatага tcttcgatca attctctctc 360
caaggggccc gcaactaggc tattattcat aaaacacaac tgaanagggg attggtttta 420
ctggtaaatc atgtgntgct aaatcatttt ctgaacagtg gggtctaaat cantcattga 480
tttagtggca gccacctgcc cggcggccgn tcgaagccca attctgcaga tatccatcac 540
actggcggcc g 551

<210> 143
<211> 515
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(515)
<223> n = A,T,C or G

<400> 143
cgagnggccc gcccgggcag gtatcttcac aaactcaaca aaggcactac atgagacttc 60
acattcccct agtccaatag ctgacaaatt tttgcaacgt tctgcaatgc gaattaactc 120
ttcatcaagt ggccgtaatc catttgcaca cactactagt tcaaccagtc tagggcatgt 180
cattcccaca cggccaagca catctttgct tactgatctc ccaaagtaca gatgggtggc 240
aggtatttca tagcgaaaga aggggtcaaa ttcttcttca tataanaaaa aatacatcac 300
taagttcact ttgggtgaat gtctgatgaa agcatcccag ctactcttct gaatagtatg 360
gaagtgtgtc tgtccaggat tctcactgac tacatcaatg cgcaaatgtt ctaatcgaac 420
atgtttttca gaagacaatg caagtaacaa ctcatcactc aataagtggt aagttcaggg 480
ctagttctct taagccgnga cactgatcag cacac 515

<210> 144
<211> 247
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(247)
<223> n = A,T,C or G

<400> 144
tgcattctct ntggatgcan acctgcccgt tggtagggac tntgctcaca cggaacatgg 60
acggttacac ctgtgccgtg ggtgacgtcc accagcttct ggatcatctc ggcgngggtg 120
ttgtggaagg gcagactatc cacctccatg cncacgatgc ccganacgcc actccggact 180
ntgtgctgca ccaanatgcc cagcattnta tcttcaagca nagcacttat cagggtcctt 240
ggcacac 247

<210> 145
<211> 309
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(309)
<223> n = A,T,C or G

<400> 145
cgtgggtcgc ggcccgangt ctgctgtaac aaaacaccat agtctgggca gctcatagac 60

aatggaattt tatttctcac gcttctggag gctggattcc aagatcaagg ttccaggaga 120
ctcagtgtct ggcaaggtct cggtttctgc ctcanagatg gtgccatctg gctgtgtcct 180
cacaagtagg aaggtgcaag aagctcccct caggctctgt ctgtaagaca ctgatcccat 240
tcatganggg gaaacgtaat gacctaatca gcccccagag accccacttc taacaccatc 300
accttgggg 309

<210> 146
<211> 486
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(486)
<223> n = A,T,C or G

<400> 146
agcgtgggtc gcggcncgac gtcctgtcca tatttcacag cccgagaact aatacaagat 60
gctgacatca tattttgtcc ctacaactat cttctanatg cacaaataag ggaaagtatg 120
gatttaaatc tgaaagaaca ggttgtcatt ttanatgaag ctcataacat cgaggactgt 180
gctcgggaat cagcaagtta cagtgtaaca gaagttcagc ttcggtttgc tcgggatgaa 240
ctanatagta tggtcaacaa taatataagg aaganagatc atgaacccct acgagctgtg 300
tgctgtagcc tcattaattg gntagaagca aacgctgaat atcttgnana angagantat 360
gaatcagctt gtaaaatatg gagtggaaat gaaatgctct taactttaca caaaatgggt 420
atcaccactg ctacttttcc cattttgcng gtaagatatn ttttctacct gngaaacgta 480
tttaag 486

<210> 147
<211> 430
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(430)
<223> n = A,T,C or G

<400> 147
gccgcccggg cangttcgac attacntnga gttccatgat gtacaattct ttcacgaaaa 60
acaatgaatg caagaatttg aggatctcct tactcctccc ttttacagat ggtctctcaa 120
tcccttcttc ttcctcttca tcttcatctt cttctgaacg cgctgccggg taccacggct 180
ttctttgtct ttatcgtgag atgaaggtga tgcttctgtt tcttctacca taactgaaga 240
aatttcgctg caagtctctt gactggctgt ttctccgact tcgcctttnt gtcaaacgng 300
agtcttttta cctcatgccc ctcagcttca cagcatcttc atctggatgt tnatttctca 360
aagggctcac tgaggaaact tctgattcan atgtcgaana gcactgtgaa gttttctctt 420
cattttgctg 430

<210> 148
<211> 483
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(483)
<223> n = A,T,C or G

<400> 148
cccgggcagg tctgtgttgn tttncaaccg gtgtcctccc cagcgtccag aananggaaa 60
tgtggagcgg gtgatgatga cccctcgctg tcctgtcacc tcctgcacag cttcgtatgt 120
gggtctggtc tgggaccacc cgtacaggtt gtgcacgttg tagtgctcca cgggggagct 180
gtccggcagg atctgctgac tctccatgca cagagtcttg ctgctcaggc ccttgtccct 240

agattccaaa tatggcatat agggtggggt tatttagcat ttcattgctg cagcccctga 300
cagatccatc cacaaaattt gatggctcat tcatatcaat ccacaatcca tcaaacttca 360
agctcttctc tggntctcga nggtttgcat agaactcttc tatctctttc ttccaccacg 420
canacctcgg ncgcgaccac gctaagccga attctgcana tatccatcac actggcggcc 480
gct 483

<210> 149
<211> 439
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(439)
<223> n = A,T,C or G

<400> 149
ctttcacgaa nacaatgaat gcaagaattt gaggatctcc ttactcctcc cttttacaga 60
tggtctctca atcccttctt cttcctcttc atcttcatct tcttctgaac gcgctgccgg 120
gtaccacggc tttctttgtc tttatcgtga gatgaaggtg atgcttctgt ttcttctacc 180
ataactgaag aaatttcgct gcaagtctct tgactggctg tttctccgac ttcgcctttt 240
tgcaaacgtg agtcttttta cctcatgccc ctcagcttcc acagcatctt catctggatg 300
ttcatttctc aaagggctca ctgaggaaac ttctgactca catgtcgaag aagcactgng 360
agtttctctt catttgctgc aaanttgctc tttgctggct gngctctcag accacccatt 420
tggctgcatg ggggctgac 439

<210> 150
<211> 578
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(578)
<223> n = A,T,C or G

<400> 150
ggcncgcccg ggcangtcca ctccactttt gagctctgag ggaatacctt caggagggac 60
agggtcaggg agtcctggca gctccgcagc agagattcac attcattcag agacttgttg 120
tccagtgcaa tgccattgat cgcaacgatc ctgtctccca cagcaaggga cccttcttta 180
gcggcagggc ttccaggcag cacagcggca gcatacactc cattctccag actgatgcca 240
ctgtctttct gtccactgan gttgatgtgc agcggcgtga ccaccttccc acccagggac 300
ttcctccgcc gcacgaccat gttgatgggc cccctnccca ttgaggagcg ccttgatggc 360
ctgcttcttg nccttggtga tgaagtccac atcggtgatt ctcacagcca gtcattgacc 420
cttaagcggn catcagcaat gcttcctttg gccactttag ngacaaatat gccacagtcc 480
ccgggaaaca agggtcattc acaccttctg gcatatcaaa cacctcggcc gggancacta 540
agccgaattc tgcagatatc catcacactg gngggccg 578

<210> 151
<211> 503
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(503)
<223> n = A,T,C or G

<400> 151
cgagcggccc gcccgggcag gtctgggaga tcagcgactg ctgccacgtg cccagaaatg 60
gctcgtcctt tcactacagc ggaatgcaat gagggtgggt gagaagatga tgggtcggtt 120
atttcattcc ttttcttttt acaacttcac tttcagagac ttcagcgttc catgtctgct 180

gtgctgtgga acccagagtg ctcttgcctg gatggctgag aatcccttgg accctggaag 240
cacctactcc atgatggccc ggtatagtgc aggctcaata taatcttccc ggtatcttga 300
gttgataact cgttgccgtt tcttttcttg cttaacctct ttctctgtga aaatctcatt 360
gaagcgcatg tctgaagcta ctgacagtct anatttgact ctcttgggaa gctcttcatc 420
cagtgtgtat acatcatctc tcttaaccac aagttggagc catncttaaa cttcacctgg 480
tacatttgga tagggtggga ggc 503

<210> 152
<211> 553
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(553)
<223> n = A,T,C or G

<400> 152
agcgtggtcg cggcccgagg tccactgagc tccgccttcc ccgggctccc tgaggaagca 60
gagtcctgac ttccaggaag gacaggacac agaggcaaga actcagcctg tgaggctctg 120
ggtggctcct gaggccagag gacgccttcc gcgatccatg gctcagcatc gtccttctgg 180
cttcccagcc ccgggccgaa cgttcgggtt aataagcaga gcagttattc ggctcctggc 240
aggagctccc ccgttagttt ccacgttgtg agcacattca tacttaagac tgnttctctt 300
tgtgttttaa gcgtctgtct ctgtagtaaa ctgaaatgtt aacagaaatg cagacctgcc 360
cgggcggccg ctcgaaagcc gaattctgca gatatccatc acactggcgg ccgctcgagc 420
atgcatctag anggcccaat tcgccctata gtgagtcgna ttacaattca ctgggccgcg 480
ntttacaacg tcgtgactgg gaaaaccctg cggtacccac ttaatcgcct tgcagnacat 540
ccccctttcg cca 553

<210> 153
<211> 454
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(454)
<223> n = A,T,C or G

<400> 153
tcgagcggct cgcccgggca ggtccaccta gcatggctcc tctaaacacg caactcagcg 60
aggggacccc cttcacctct ggcaagagag ctgggtagat cagaaacttg gtgacacctg 120
gctagcacag agcaggctca cttgtcttgg tcccactacc cagattcctg cagacattgc 180
aaaccaaatg aaggttgntg aatgacccct gtccccagcc acttgttttg gtatcatctg 240
ctctgcagtg gaatgcctgt gtgtttgagt tcactctgca tctgtatatt tgagtataga 300
aaccgantca agtgatctgt gcatncagac acactggggc acctgancac agaacaaatc 360
accttaacga tctggaatga aactgnganc antgcccgcc tgggtgggtc tgganaaact 420
gccgncttct tgttggacct tggccgcacc acct 454

<210> 154
<211> 596
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(596)
<223> n = A,T,C or G

<400> 154
agcgtggtcg cggcccgang gcggcctcct gantganggg aagggacgtg ggggcggcca 60
cggcaggatt aacctccatt tcagctaatc atgggagaga ttaaagtctc tcctgattat 120

aactggttta naggtacagt tccccttaaa aagattattg tggatgatga tgacagtaag 180
atatggtcgc tctatgacgc gggcccccga agtatcaggt gtcctctcat attcctgccc 240
cctgtcagtg gaactgcaga tgtctttttc cggcagattt tggctctgac tggatggggt 300
taccgggtta tcgctttgca gtatccagtt tattgggacc atctcgagtt cttgtgatgg 360
attcacaaaa cttttanacc atttacaatt ggataaagtt catcttttg gcgcttcttt 420
gggangcttt ttggcccana aatttgctga atacactcac aaatctccta gaagccattc 480
cctaatcctc tgcaattcct tcagngacac ctctatcttc aaccaacttg gactggaaac 540
agctttggct gatgcctgca tttatgctca aaaaatagtt cttggaaatt ttcatc 596

<210> 155
<211> 343
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(343)
<223> n = A,T,C or G

<400> 155
ctcganttgg cncgcccggg cangtctgcc tggtttttga ccgngcgagc tatttagnct 60
ctggctctgt ttccggagct caaggnaaaa atcttgaana actcgagcag cttctgtgga 120
tagccttggg tacacatact gccgagcata gccaatgtac tttctcaata gctggtgggg 180
aatgggatct attgtttctc caggaaccac ctttagtctt tctgataatg gcttctcaga 240
aactacttca agtacggaag tatttgaatc ttgactatnc atacgagcta ctgtggcact 300
gctaatgggn tctctgctnt ccagctctta ttgcaatcac atg 343

<210> 156
<211> 556
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(556)
<223> n = A,T,C or G

<400> 156
tcgagcggcc cgcccgggca ggtctggcac cacncagatc gattaactgg ctcatctgat 60
ctcgtggccc ccaccctgga actgacttag cacaaaagga cacctcaatt ccttatgatt 120
tcatctccga cccaaccaat caacaccctt gactcactgg ccttcccccc cccaccaaat 180
tatccttaaa aactctgatc cccgaatgct cagggagatc gatttgagta ctaataagac 240
tccagtctcc tgcacaagca gctctgtgta ctcttcctct attgcaattc ctgtcttgat 300
aaatcggctc tgtgtaggcg gcggaagaag tgaacctgtt gggcggttac cacctctgtc 360
gtgtgtgaca gttgntttga atctctaatt gctcagtaca gatccacatg caggttaagt 420
aagaagcttt tgaagaaaat ggaaagtctt aagtgatggc ttccaagaaa tcaaacctac 480
attaattagg gaacaacgga ctttacgtat cacaaatgaa gagactgacn aagtaaatca 540
acttggcctt ttctta 556

<210> 157
<211> 333
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(333)
<223> n = A,T,C or G

<400> 157
ggtccacaaa aatatatnaa ataagctgga tatataaaan caaacactta acatngncan 60
cattccttca gttattcaaa ctcactgata nctaacnggg agnagttggn attctggaag 120

acttcctaag ctaaaagtat atttacatat ttacaacaca ngtaaatata acngaagaac 180
tacttcaaat aangnngaaa ttccagaatt ctanagattt atagctatag ntnacaanta 240
tcaccaattg gtttgcaatc aanngnccag cactacttat gannaangtt taactannaa 300
accaaaaggg gagaaaacct ggnagggaaa nat 333

<210> 158
<211> 629
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(629)
<223> n = A,T,C or G

<400> 158
tcgagcggcc gcccgggcag gtctggtaca tttgtgcgag gtccggcact ctgttctcat 60
ccagtaagtg gtcgagccct ttctgcagaa ttgctgttaa atgttctcct aatagctgtt 120
tctccacaca agcaatcagt ggtttctgtg tgctgtggtc caagtaagtg attactctgt 180
ctccctcttc ttctaagcgt ttacttacat ggttaagata ttctggaacc tctctttcct 240
gcattaacct ttggccttcg gcagcatata agcaattagt ctcttccaaa aatttcagtt 300
caaatgaatc tttatacacc tgcaggtcag acagcatgcc caggnaggct ccgcaacagg 360
ctccggtcca cggcctcgcc gctcctctcg cgctcgatca gcagtaggat tccatcaatg 420
gttttactct gaaccatttt atcactaata atatgggttc taaacagttc taatcccata 480
tcccagatgg agggcagcgt ggagttctgc agcacatagg tgcggtccaa gaacaggaag 540
atgcttctga tcatgaatca tttgnctggc aatggtcctg ccagcacgtg gtaatctttc 600
ttttaaaaat aaacccttat ctaaacgtc 629

<210> 159
<211> 629
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(629)
<223> n = A,T,C or G

<400> 159
tcgagcggcc gcccgggcag gttctagagg ganaatctgg ctgatttggg aataaaatat 60
aatcgaatat tcaacaccat gaagataaat cttattttgg aaatctactg accttaatac 120
cccaagcttg ccctgaatac tttgattgga attggaatat atcaaaaaag gttagtattt 180
ttgttgtagt taggatacta aaaggatatt agttacccaa gagatccaat ttgtttttct 240
gatgaatagt gttcagtaaa atgaagcagt cttaagagtg actaataatt tcaaagtgat 300
ttttcgtcta ttcttaatat tttttaatta tttatttta agagttttat accttgagca 360
gatacaatga tccgctttag tgagaggaca atttctgatt gattgttttc tcttcaggcc 420
atctcacctc ttcattctct tgttacattt gaagcagttg atataatggg tttatacttt 480
aaaagataga catggtgcca tgaagtttgg ggaagttggg tgaattatcc cattctagtt 540
acagangagc tttccttaaa tgccctttac ttctangttt ggtcaagaag tcattttctg 600
agtaaaagtt attttcatat atgttgggg 629

<210> 160
<211> 519
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(519)
<223> n = A,T,C or G

<400> 160

tcgagcggcg cgcccgggca ggtctgctgg gattaatgcc aagttnttca gccataaggt 60
agcgaaatct agcagaatcc agattacatc cacttccaat cacgcggtgt ttgggtaatc 120
cacttagttt ccagataaca tacgtaagaa tgtccactgg gttggaaacc acaattatga 180
tgcaatcagg actgtacttg acgatctgag gaataatgaa tttgaagaca ttaacatttc 240
tctgcaccag attgagccga ctctcccctt cttgctgacg gactcctgca gttaccacta 300
caatcttana attgggcggg tcacagaata atctttatct gccacaattt taggtgctga 360
agaaataagc tcccatgctg cagatccatc atttctnctt taagcttatc ttccaaaaca 420
tccacaagan caangttcat cagccagaga ctttcccaga atgctgatag nacacgccat 480
accaacttgt ccaacancca ctacagcgat cttattggt 519

<210> 161
<211> 446
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(446)
<223> n = A,T,C or G

<400> 161
cgagnggccc gcccgggcag gtccagtaag cntttnacga tgatgggaaa ggttatgcaa 60
ggtcccagcg gtacaacgag ctgtttctac atcatttgta ttctgcatgg tacgtacaat 120
agcagacacc atctgaggag aacgcatgat agcgtgtctg gaagcttcct ttttagaaag 180
ctgatggacc ataactgcag ccttattaac caccacctgg tcctcgtcat ttagcagttt 240
tgtcagttca gggattgcac gtgtggcang ttctgcatca tcttgatagt taatcaagtt 300
tacaactggc atgtttcagc atctgcgatg ggctcagcaa acgctggaca ttantgggat 360
gagcagcatc aaactgtgta natgggatct gcatgccctc atctaatgtc tcagggaaca 420
tagcagctcg taccctctga gctcga 446

<210> 162
<211> 354
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(354)
<223> n = A,T,C or G

<400> 162
agcgtngtcg cggcccgang tcctgggaag cctttnttgc tgagcctcac agcctctgtc 60
aggcggctgc ggatccagcg gtccaccagg ctctcatggc ctccgggctg ggaggngggt 120
gagggcacaa aacccttccc aaggccacga anggcaaact tggtggcatt ccanagcttg 180
ttgcanaagt ggcggnaacc cagtatccgg ttcacatcca ggntgatgtc acgaccctgg 240
gacatgtang cacataatcc aaaccggaga gcatcggtgc cacattcacg aatccccgct 300
gggaagtcag ctttctgccc ttctttggcc ttctccacct cgctgggatc cagg 354

<210> 163
<211> 258
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(258)
<223> n = A,T,C or G

<400> 163
tttttcncca agtcctcttg ccgngggatc tngactgcaa tttaagacac ttctaattag 60
ttatacccag gccctgcaaa attgctgggt ttatataata tattcttgct gcacgaagat 120
ttattattct gttggatgat tctattttaa ttntatttat tctggccaaa aaagaacctt 180

ctccgctcgt caagagangc caatntgtct tgaaggacaa gagaaagatg ctaacacaca 240
ctttcttctt cttgagga 258

<210> 164
<211> 282
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

<400> 164
ggaacatatt acttttaaat tacttgggtc aatgaaacat ttaataaaaa catttgcttc 60
tctatataat acgtatgtat aaaataagcc ttttcanaaa ctctggttct cataatcctc 120
tataaatcan atgatctgac ttctaagagg aacaaattac agnaaggggt atacattnat 180
gaatactggt agtactagag ganngacgct aaaccactct actaccactt gcggaactct 240
cacagggtaa atgacaaagc caatgactga ctctaaaaac aa 282

<210> 165
<211> 462
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(462)
<223> n = A,T,C or G

<400> 165
gcccgggcan gtcctgtaat cccagctact cangangctg agtcatgana atcgcctgaa 60
tccgggaggt agaggccgca gcgagcaaag attaagccac tgcactccag tctgggtgac 120
agagtgagaa tctgtctgtt gctcctctgg cattggtctg aaatgggttt gtagaacatg 180
ccacagaagg accagcanca gcaacaaatg gatttgtgga angcgtagct ccaaatggag 240
cangcacact tgatgaagca cgctgtgtct gtgcagangc aaccactggc actgttccaa 300
aaacattgct gctagcatta cttgtggaag tatacgcatt actggaggtg gctgcanaac 360
tgaaaacgct gtctagttct gccanagctg catacttgnc tgaanatgca cttgactgac 420
tgggaactga accacanaac caacaggacc tttacctgtg ga 462

<210> 166
<211> 365
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(365)
<223> n = A,T,C or G

<400> 166
cgtgggtcgc ggcncgangt ctgaaaccaa tccagaacta aacatcagca cacaaaaaat 60
accaggatag atggaatcaa aagactctga agccaaaagg aggctaggga gagcaactga 120
acttagcaag ctgaggactt cagtgtccat catccgatcc tgccctgtaa caacaggtct 180
atatgataga gatattccat ctgagctgga ggccattatc cttagcaaac taacacagaa 240
cagaaaacca aatacatgtt ctcatttaga agtaggagct aaatgatgag aactcaagga 300
cacaaagaaa ggaacaacag acactggggc ctacttgagg gtggagggtg ggaggaggga 360
gaaga 365

<210> 167
<211> 364
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(364)
<223> n = A,T,C or G

<400> 167
agcgtggtcg cggcgcgang tccagcccta gcttgcctgt gactccgcct tcactgggtg 60
ctctctctaa aagttgctga ctctttactg tatctcccaa ttcccactcc attggttcca 120
taaggggagg ggtgtctcac tcaacatggt gttcctggta ccaagaactg gctgacgaag 180
ctgggtgccg tggctcatgc ctgtaatccc agcacttttg ggaggccaag aagggcggat 240
cacctgaggt ctggagttca agatcagcct gaccaacatg atgaaaccaa gtctccacta 300
aaaatataaa acaattagcc aggcatggtg gtgggtgcct gnaatcccag ctactgggga 360
ngct 364

<210> 168
<211> 447
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(447)
<223> n = A,T,C or G

<400> 168
cccgggcagg tcaaaaccca aaacctttca ttttagccca aaccagctca tgattaggta 60
tacaaggata acagaaccag ttgtcaggac gagcatttga caagtaaaag caattcttgc 120
aaagctgcag ttcatccagc tcatggcatg tgtctttata tagcatcctc gcaatgtcag 180
cttgctcact gtctgctcca tagaaaatca cggtattgtg gagaagcaat tgggcatcag 240
ctttgaactc ttcataactt cggtatttcc cttcattcac tttctcttga atggtgggaa 300
cgtccacaga cctcggccgc gaccacgcta agcccgaatt ctgcagatat ccatcacact 360
ggcggccgtt cgagcatggc atctagaagg cccaattcgc ctatagngag tcgnattacc 420
aattcactgg ccgtcgnttt acaacgc 447

<210> 169
<211> 524
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(524)
<223> n = A,T,C or G

<400> 169
cgantngcgc gcccgggcag gtctgagcag cctttctgnn tgctggacta ttgggattgg 60
gttcatccaa cagagactgt atggatgtta gaatggaaga cacatcatag gttggactcc 120
aacggttctg aagtatgtcc agacatatac taccatctgc atagactaag aacaaagaag 180
taggtacatt aaacgtaaca agaccactaa ggttttaaca ttatagacaa aacanaaata 240
gtcaaganta ctttgctttt gaagtttaaa gattcctatg ttgcttccca gttaactgcc 300
taaaaagata agncataacc accactagtg aaataatcan gatgatcaga gaatgtcana 360
tgtgatcagt ataaaactgg angatattna gtgtcatcct ttggaaaagg ctgccctatn 420
atccaggaaa tcanaaacat tnttgaacag ggnccctagc tatccacaga catgtgggaa 480
attcattccc caaatngtag gctggatccc ctatctgaaa taac 524

<210> 170
<211> 332
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(332)
<223> n = A,T,C or G

<400> 170
tcgancggcn cgcccgggca ggtgacaaac ctgttattga agatgttggt tctgatgagg 60
aanaanatca gaagggatgg tgacaagaan aanaanaaga agattaagga aaagtacatc 120
gatcaagaag agctcaacaa aacaaagccc atctggacca gaaatcccga cgatattact 180
aatgangagt acggagaatt ctataanagc ttgaccaatg actgggaaga tcacttggca 240
gtgaagcatt tttcagttga nggacagttg gaattcagag cccttctatn tgtcccacga 300
cgtgctcctt ttgatctgtt tganancaga aa 332

<210> 171
<211> 334
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(334)
<223> n = A,T,C or G

<400> 171
cgagnggcnc gcccgggcag gtctgttgat agcgacttaa cagaaaagtc tagacaaaca 60
taagcataaa aaattacagt ctttctaccc ttgggaatgg ggagaaaaag gaatctctac 120
cccaagacca gaaataataa gtcctgtttc tggtcctgaa catccagaat tatggaggct 180
ttggcctgac accacattan aatttggtct ggaaatcaaa ctttaganac angagatcgt 240
aagccatttt atactatcga cctaaattcc agtctaacgg ttcctttaca aagttgcgga 300
aagccctctt atatgctagc tgtaggaaat atag 334

<210> 172
<211> 439
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(439)
<223> n = A,T,C or G

<400> 172
agcgtggtcg cggcccgang tctgcctata aaactagact tctgacgctg ggctccagct 60
tcattctcac aggtcatcat cctcatccgg gagagcagtt gtctgagcaa cctctaagtc 120
gtgctcatac tgtgctgcca aagctgggtc catgacaact tctggtgggg cgagagcagg 180
catggcaaca aattccaagt tagggtctcc aatgagcttc ctagcaagcc agaggaaggg 240
cttttcaaag ttgtagttac ttttggcaga aatgtcgtag tactgaagat tcttctttcg 300
gtggaagaca atggatttcg ccttcacttt ctgccttaat atccactttg gtgccacaca 360
acacaatggg gatgntttca cacacttngn accanatctc tatgccagnt aggccatttt 420
ggaagnactt cganggtac 439

<210> 173
<211> 599
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(599)
<223> n = A,T,C or G

<400> 173

cgatnggccg cccgggcagg tcctgtaaaa naggaaattc agacatcgta cgactcgtaa 60
ttgaatgtgg agctgactgc aatattttgt caaagcacca gaatagtgcc ctgcactttg 120
cgaagcagtc taacaatgtg cttgtgtacg acttgctgaa gaaccattta gagacacttt 180
caagagtagc agaagagaca ataaaggatt actttgaagc tcgccttgct ctgctagaac 240
cagtttttcc aatcgcatgt catcgactct gtgagggtcc agatttttca acagatttca 300
attaccaacc cccacagaac ataccagaag gctctggcat cctgctgttt atcttccatg 360
caaacttttt gggtaaagaa gttattgctc ggctctgtgg accgtgtagt gtacaagctg 420
tagttctgaa tgataaattt cagcttcctg tttttctggg tctcgctctg ttgtccaggc 480
tggagtgcag tggcgcggat tacagctcac tggagtcttg acttcccagg cacaagcaat 540
cctcccacct cagcctccta actacctggg actaaaaatg caccgccacc acattccgg 599

<210> 174
<211> 458
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(458)
<223> n = A,T,C or G

<400> 174
tcgatttggc cgcccgggca ggtccatgcn gnttntgccc attcccatgg ngcccgacaa 60
ncccatcccc gaggccgaca tccccatgtt catgttcatg cccaccatgc cctggctcat 120
ccctgcgctg ttccccagag gggccattcc catggtgccc gtcattacac cgggcatgtt 180
cataggcatg ggtcccccca ggagagggtt agnttgaggc cggacaggaa gcatgtttga 240
tggagaactg aggttcacag nctccaaaac tttgagtcat cacattcata ggctgctgca 300
tattctgtct gctgaatcca ttgtatncag tgatggcctg ctggggnttt ggaaggctng 360
cataccaggt agtaagntcg tctaggctga tgtttacacc tggggtcaga ccaagtanga 420
gggcaaggtt ttgctgactg attttctgga cccatatc 458

<210> 175
<211> 1206
<212> DNA
<213> Homo sapien

<400> 175
ggcacgagga agttttgtgt actgaaaaag aaactgtcag aagcaaaaga aataaaatca 60
cagttagaga accaaaaagt taaatgggaa caagagctct gcagtgtgag gtttctcaca 120
ctcatgaaaa tgaaaattat ctcttacatg aaaattgcat gttgaaaaag gaaattgcca 180
tgctaaaact ggaaatagcc acactgaaac accaatacca ggaaaaggaa aataaatact 240
ttgaggacat taagatttta aaagaaaaga atgctgaact tcagatgacc ctaaaactga 300
aagaggaatc attaactaaa agggcatctc aatatagtgg gcagcttaaa gttctgatag 360
ctgagaacac aatgctcact tctaaattga aggaaaaaca agacaaagaa atactagagg 420
cagaaattga atcacaccat cctagactgg cttctgctgt acaagaccat gatcaaattg 480
tgacatcaag aaaaagtcaa gaacctgctt tccacattgc aggagatgct tgtttgcaaa 540
gaaaaatgaa tgttgatgtg agtagtacga tatataacaa tgaggtgctc catcaaccac 600
tttctgaagc tcaaaggaaa tccaaaagcc taaaaattaa tctcaattat gccggagatg 660
ctctaagaga aaatacattg gtttcagaac atgcacaaag agaccaacgt gaaacacagt 720
gtcaaatgaa ggaagctgaa cacatgtatc aaaacgaaca agataatgtg aacaaacaca 780
ctgaacagca ggagtctcta gatcagaaat tatttcaact acaaagcaaa aatatgtggc 840
ttcaacagca attagttcat gcacataaga aagctgacaa caaaagcaag ataacaattg 900
atattcattt tcttgagagg aaaatgcaac atcatctcct aaaagagaaa aatgaggaga 960
tatttaatta caataaccat ttaaaaaacc gtatatatca atatgaaaaa gagaaagcag 1020
aaacagaagt tatataatag tataacactg ccaaggagcg gattatctca tcttcatcct 1080
gtaattccag tgtttgtcac gtggttgttg aataaatgaa taaagaatga gaaaaccaga 1140
agctctgata cataatcata atgataatta tttcaatgca caactacggg tggtgctgct 1200
cgtgcc 1206

<210> 176
<211> 317
<212> PRT

<213> Homo sapien

<400> 176

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            20                  25                  30
Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
        35                  40                  45
Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
    50                  55                  60
Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg
65                  70                  75                  80
Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr
                85                  90                  95
Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu
            100                 105                 110
Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp
        115                 120                 125
His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His
    130                 135                 140
Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser
145                 150                 155                 160
Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala
                165                 170                 175
Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp
            180                 185                 190
Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln
        195                 200                 205
Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn
    210                 215                 220
Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp
225                 230                 235                 240
Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln
                245                 250                 255
Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile
            260                 265                 270
Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu
        275                 280                 285
Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile
    290                 295                 300
Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Val Ile
305                 310                 315
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<210> 177
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in the Lab

<400> 177
ccaatcatct ccacaggagc 20

<210> 178
<211> 1665
<212> DNA
<213> Homo sapien

<400> 178
gcaaactttc aagcagagcc tcccgagaag ccatctgcct tcgagcctgc cattgaaatg 60

caaaagtctg ttccaaataa agccttggaa ttgaagaatg aacaaacatt gagagcagat 120
cagatgttcc cttcagaatc aaaacaaaag aaggttgaag aaaattcttg ggattctgag 180
agtctccgtg agactgtttc acagaaggat gtgtgtgtac ccaaggctac acatcaaaaa 240
gaaatggata aaataagtgg aaaattagaa gattcaacta gcctatcaaa aatcttggat 300
acagttcatt cttgtgaaag agcaagggaa cttcaaaaag atcactgtga acaacgtaca 360
ggaaaaatgg aacaaatgaa aaagaagttt tgtgtactga aaaagaaact gtcagaagca 420
aaagaaataa aatcacagtt agagaaccaa aaagttaaat gggaacaaga gctctgcagt 480
gtgaggtttc tcacactcat gaaaatgaaa attatctctt acatgaaaat tgcatgttga 540
aaaaggaaat tgccatgcta aaactggaaa tagccacact gaaacaccaa taccaggaaa 600
aggaaaataa atactttgag gacattaaga ttttaaaaga aaagaatgct gaacttcaga 660
tgaccctaaa actgaaagag gaatcattaa ctaaaagggc atctcaatat agtgggcagc 720
ttaaagttct gatagctgag aacacaatgc tcacttctaa attgaaggaa aaacaagaca 780
aagaaatact agaggcagaa attgaatcac accatcctag actggcttct gctgtacaag 840
accatgatca aattgtgaca tcaagaaaaa gtcaagaacc tgctttccac attgcaggag 900
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aaaaagagaa agcagaaaca gaaaactcat gagagacaag cagtaagaaa cttcttttgg 1440
agaaacaaca gaccagatct ttactcacaa ctcatgctag gaggccagtc ctagcattac 1500
cttatgttga aaatcttacc aatagtctgt gtcaacagaa tacttatttt agaagaaaaa 1560
ttcatgattt cttcctgaag cctgggcgac agagcgagac tctgtctcaa aaaaaaaaaa 1620
aaaaaaagaa agaaagaaat gcctgtgctt acttcgcttc ccagg 1665

<210> 179
<211> 179
<212> PRT
<213> Homo sapien

<400> 179
Ala Asn Phe Gln Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
1 5 10 15
Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
20 25 30
Asn Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro Ser Glu Ser Lys
35 40 45
Gln Lys Lys Val Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu
50 55 60
Thr Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala Thr His Gln Lys
65 70 75 80
Glu Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser
85 90 95
Lys Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln
100 105 110
Lys Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys
115 120 125
Lys Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys
130 135 140
Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser
145 150 155 160
Val Arg Phe Leu Thr Leu Met Lys Met Lys Ile Ile Ser Tyr Met Lys
165 170 175
Ile Ala Cys

<210> 180
<211> 1681
<212> DNA

<213> Homo sapien

<400> 180

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caggaaaaat ggaacaaatg aaaaagaagt tttgtgtact gaaaaagaaa ctgtcagaag     120
caaaagaaat aaaatcacag ttagagaacc aaaaagttaa atgggaacaa gagctctgca     180
gtgtgagatt gactttaaac caagaagaag agaagagaag aaatgccgat atattaaatg     240
aaaaaattag ggaagaatta ggaagaatcg aagagcagca taggaaagag ttagaagtga     300
aacaacaact tgaacaggct ctcagaatac aagatataga attgaagagt gtagaaagta     360
atttgaatca ggtttctcac actcatgaaa atgaaaatta tctcttacat gaaaattgca     420
tgttgaaaaa ggaaattgcc atgctaaaac tggaaatagc cacactgaaa caccaatacc     480
aggaaaagga aaataaatac tttgaggaca ttaagatttt aaaagaaaag aatgctgaac     540
ttcagatgac cctaaaactg aaagaggaat cattaactaa aagggcatct caatatagtg     600
ggcagcttaa agttctgata gctgagaaca caatgctcac ttctaaattg aaggaaaaac     660
aagacaaaga aatactagag gcagaaattg aatcacacca tcctagactg gcttctgctg     720
tacaagacca tgatcaaatt gtgacatcaa gaaaaagtca agaacctgct ttccacattg     780
caggagatgc ttgtttgcaa agaaaaatga atgttgatgt gagtagtacg atatataaca     840
atgaggtgct ccatcaacca ctttctgaag ctcaaaggaa atccaaaagc ctaaaaatta     900
atctcaatta tgccggagat gctctaagag aaaatacatt ggtttcagaa catgcacaaa     960
gagaccaacg tgaaacacag tgtcaaatga aggaagctga acacatgtat caaaacgaac    1020
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tacaaagcaa aaatatgtgg cttcaacagc aattagttca tgcacataag aaagctgaca    1140
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taaaagagaa aaatgaggag atatttaatt acaataacca tttaaaaaac cgtatatatc    1260
aatatgaaaa agagaaagca gaaacagaaa actcatgaga gacaagcagt aagaaacttc    1320
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cttgttcacg aattgcataa aagctgccca ggatttccat ctaccctgga tgatgccgga    1560
gacatcattc aatccaacca gaatctcgct ctgtcactca ggctggagtg cagtgggcgc    1620
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<210> 181
<211> 432
<212> PRT
<213> Homo sapien

<400> 181

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Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys Phe Cys
            20                  25                  30
Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu
        35                  40                  45
Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu
    50                  55                  60
Thr Leu Asn Gln Glu Glu Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn
65                  70                  75                  80
Glu Lys Ile Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His Arg Lys
                85                  90                  95
Glu Leu Glu Val Lys Gln Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp
            100                 105                 110
Ile Glu Leu Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser His Thr
        115                 120                 125
His Glu Asn Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys
    130                 135                 140
Glu Ile Ala Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr
145                 150                 155                 160
Gln Glu Lys Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu
                165                 170                 175
Lys Asn Ala Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu
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            180                 185                 190
Thr Lys Arg Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala
        195                 200                 205
Glu Asn Thr Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu
    210                 215                 220
Ile Leu Glu Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala
225                 230                 235                 240
Val Gln Asp His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro
                245                 250                 255
Ala Phe His Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val
            260                 265                 270
Asp Val Ser Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu
        275                 280                 285
Ser Glu Ala Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr
    290                 295                 300
Ala Gly Asp Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln
305                 310                 315                 320
Arg Asp Gln Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met
                325                 330                 335
Tyr Gln Asn Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu
            340                 345                 350
Ser Leu Asp Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu
        355                 360                 365
Gln Gln Gln Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys
    370                 375                 380
Ile Thr Ile Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu
385                 390                 395                 400
Leu Lys Glu Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys
                405                 410                 415
Asn Arg Ile Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Asn Ser
            420                 425                 430
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<210> 182
<211> 511
<212> DNA
<213> Homo sapiens

<400> 182
gaagtttcat gaggtttagc ttttctgggc tggggagtgg agagaaagaa gttgcagggc 60
ttacaggaaa tcccagagcc tgaggtttc tcccagattt gagaactcta gattctgcat 120
cattatcttt gagtctatat tctcttgggc tgtaagaaga tgaggaatgt aataggtctg 180
ccccaagcct ttcatgcctt ctgtaccaag cttgtttcct tgtgcatcct tcccaggctc 240
tggctgcccc ttattggaga atgtgatttc caagacaatc aatccacaag tgtctaagac 300
tgaatacaaa gaacttcttc aagagttcat agacgacaat gccactacaa atgccataga 360
tgaattgaag gaatgttttc ttaaccaaac ggatgaaact ctgagcaatg ttgaggtgtt 420
tatgcaatta atatatgaca gcagtctttg tgatttattt taactttctg caagaccttt 480
ggctcacaga actgcagggt atggtgagaa a 511

<210> 183
<211> 260
<212> DNA
<213> Homo sapiens

<400> 183
cacctcgcgg ttcagctcct ctgtcttggt gaagaaccat tcctcggcat ccttgcggtt 60
cttctctgcc atcttctcat actggtcacg catctcgttc agaatgcggc tcaggtccac 120
gccaggtgca gcgtccatct ccacattgac atctccaccc acctggcctc tcagggcatt 180
catctcctcc tcgtggttct tcttcaggta ggccagctcc tccttcaggc tctcaatctg 240
catctccagg tcagctctgg 260

<210> 184
<211> 461

<212> DNA
<213> Homo sapiens

<400> 184
gtctgatggg agaccaaaga atttgcaagt ggatggtttg gtatcactgt aaataaaaag 60
agggcctttt ctagctgtat gactgttact tgaccttctt tgaaaagcat tcccaaaatg 120
ctctatttta gatagattaa cattaaccaa cataattttt tttagatcga gtcagcataa 180
atttctaagt cagcctctag tcgtggttca tctctttcac ctgcatttta tttggtgttt 240
gtctgaagaa aggaaagagg aaagcaaata cgaattgtac tatttgtacc aaatctttgg 300
gattcattgg caaataattt cagtgtggtg tattattaaa tagaaaaaaa aaattttgtt 360
tcctaggttg aaggtctaat tgataccgtt tgacttatga tgaccattta tgcactttca 420
aatgaatttg ctttcaaaat aaatgaagag cagacctcgg c 461

<210> 185
<211> 531
<212> DNA
<213> Homo sapiens

<400> 185
tctgatttta tttccttctc aaaaaaagtt atttacagaa ggtatatatc aacaatctga 60
caggcagtga acttgacatg attagctggc atgatttttt ctttttttc ccccaaacat 120
tgtttttgtg gccttgaatt ttaagacaaa tattctacac ggcatattgc acaggatgga 180
tggcaaaaaa aagtttaaaa acaaaaaccc ttaacggaac tgccttaaaa aggcagacgt 240
cctagtgcct gtcatgttat attaaacata catacacaca atcttttgc ttattataat 300
acagacttaa atgtacaaag atgttttcca ctttttcaa tttttaaaca caacagctat 360
aaacctgaac acatatgcta tcatcatgcc ataagactaa aacaattata tttagcgaca 420
agtagaaagg attaaatagt caaatacaag aatgaaaaac gcagtacata gtgtcgcgaa 480
ctcaaatcgg catttagata gatccagtgg tttaaacggc acgtttttgc t 531

<210> 186
<211> 441
<212> DNA
<213> Homo sapiens

<400> 186
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atcaaaagaa tcatcatctt taccttgact tttcagggaa ttactgaact ttcttctcag 120
aagatagggc acagccattg ccttggcctc acttgaaggg tctgcatttg ggtcctctgg 180
tctcttgcca agtttcccaa ccactcgagg gagaaatatc gggaggtttg acttcctccg 240
gggctttccc gagggcttca ccgtgagccc tgcggccctc agggctgcaa tcctggattc 300
aatgtctgaa acctcgctct ctgcctgctg gacttctgag gccgtcactg ccactctgtc 360
ctccagctct gacagctcct catctgtggt cctgttgtac tggacggggt ccccagggtc 420
ctgggggctt ttttcctgtc t 441

<210> 187
<211> 371
<212> DNA
<213> Homo sapiens

<400> 187
aaaagtgaat gagtaactat tatattgttg gcaataataa gttgcaaaat catcaggctg 60
caggctgctg atggtgagag tgaactctgt cccagatcca ctgccgctga accttgatgg 120
gaccccagat tctaaactag acgccttatg gatcaggagc tttggggctt tccctggttt 180
ctgttgatac caggccaacc aactactaac actctgactg gcccggcaag tgatggtgac 240
tctgtctcct acagttgcag acagggtgga aggagactgg gtcatctgga tgtcacattt 300
ggcacctggg agccagagca gcaggagccc caggagctga gcggggaccc tcatgtccat 360
gctgagtcct g 371

<210> 188
<211> 226
<212> DNA
<213> Homo sapiens

<400> 188
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ttttattcct tgatattttt ctttttttttt tttttgtgga tggggacttg tgaatttttc 120
taaaggtgct atttaacatg ggaggagagc gtgtgcggct ccagcccagc ccgctgctca 180
ctttccaccc tctctccacc tgcctctggc ttctcaggac ctgccc 226

<210> 189
<211> 391
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(391)
<223> n=A,T,C or G

<400> 189
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tggattctgg gcatcgtcgg cgcatgcttg taatcctact tgggaggttg anacaggaga 120
cctcggccgc naccacgcta agggcgaatt ctgcanatat ccatcacact ggcggccgct 180
cgagcatgca tctanagggc ccaattcncc ctatagtgag ncgtattaca attcactggc 240
cgtcgtttta caacgtcgtg actgggaaaa ccctggcgtt acccaactta atcgccttgc 300
agcacatccc cctttcncca gctggcttaa tancgaagag gcccgcaccg atcgcccttc 360
ccaacanttg cgcagcctga atggcgaatg g 391

<210> 190
<211> 501
<212> DNA
<213> Homo sapiens

<400> 190
catcttggcc tttttgagct gtttccgctt cttctcatcc cggtcactgt caccctcatt 60
actggaggag ctggcagagg cgttgctgtc aaactcctct gccacatctt cctcctcttc 120
acctgggttg aatgactcat cggtttcttc tcctgagtca tcgctgctgt cattggcatt 180
ctcctcccgg atcttgcctt cctccttcat cctctccaag taggcatcat gctggtcctc 240
atcagagtca gcatattcat cgtagcttgg gttcatgccc tctttcaatc ctcggttttt 300
gatgttgagc tttttcgcgt tgacaaaatc aaacagtttc ccgtactcct ccctctcaat 360
gctgctgaag gtatactgag tgccctgctt ggtctcaatt tcaaagtcaa aggaacgagt 420
agtagtggta ccacgagcaa agttgacaaa ggagatctca tcgaagcgga tgtgcacagg 480
tggcttgtgg acgtagatga a 501

<210> 191
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (49)
<223> n=A,T,C or G

<400> 191
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aacagaaagt aaaaactaac atggattgct ataaatatgc tgaagcctag ttgttcaaat 120
gatacaattc tctcatgcta ctctaaagtt tataaagaaa aaggatttac actttacaca 180
ctgtacacaa aaggaatacc ttctgagagc cagggagtgg ggaaagggga aggagacttg 240
a 241

<210> 192
<211> 271
<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(271)
<223> n=A,T,C or G

<400> 192
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gatagaagan caaaccacgt cccacgaatc ccaataatga cagcttcaga ctttgctttt 120
ttaacaattt gaaaaattat tctttaatgt ataaagtaat tttatgtaaa ttaataaatc 180
ataatttcat ttccacattg attaaagctg ctgtatagat ttagggngca ggacttaata 240
atagnggaaa tgaaattatg atttattaat c 271

<210> 193
<211> 351
<212> DNA
<213> Homo sapiens

<400> 193
agtcgaggcg ctgatcccta aaatggcgaa catgtgtttt catcatttca gccaaagtcc 60
taacttcctg tgcctttcct atcacctcga gaagtaatta tcagttggtt tggatttttg 120
gaccaccgtt cagtcatttt gggttgccgt gctcccaaaa cattttaaat gaaagtattg 180
gcattcaaaa agacagcaga caaaatgaaa gaaaatgaga gcagaaagta agcatttcca 240
gcctatctaa tttctttagt tttctatttg cctccagtgc agtccatttc ctaatgtata 300
ccagcctact gtactattta aaatgctcaa tttcagcacc gatggacctg c 351

<210> 194
<211> 311
<212> DNA
<213> Homo sapiens

<400> 194
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caccctccct ctgctgggat gaggtccagg agccaactaa aacaatggca gaggagacat 120
ctctggtgtt cccaccaccc tagatgaaaa tccacagcac agacctctac cgtgtttctc 180
ttccatccct aaaccacttc cttaaaatgt ttggatttgc aaagccaatt tggggcctgt 240
ggagcctggg gttggatagg gccatggctg gtcccccacc atacctcccc tccacatcac 300
tgacacagac c 311

<210> 195
<211> 381
<212> DNA
<213> Homo sapiens

<400> 195
tgtcagagtg gcactggtag aagttccagg aaccctgaac tgtaagggtt cttcatcagt 60
gccaacagga tgacatgaaa tgatgtactc agaagtgtcc tggaatgggg cccatgagat 120
ggttgtctga gagagagctt cttgtcctgt ctttttcctt ccaatcaggg gctcgctctt 180
ctgattattc ttcagggcaa tgacataaat tgtatattcg gttcccggtt ccaggccagt 240
aatagtagcc tctgtgacac cagggcgggg ccgagggacc acttctctgg gaggagaccc 300
aggcttctca tacttgatga tgtagccggt aatcctggca cgtggcggct gccatgatac 360
cagcagggaa ttgggtgtgg t 381

<210> 196
<211> 401
<212> DNA
<213> Homo sapiens

<400> 196
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gcccaaacct ggagacctga ttgagatttt ccgccttggc tatgagcact gggccctgta 120

tataggagat ggctacgtga tccatctggc tcctccaagt gagtaccccg gggctggctc 180
ctccagtgtc ttctcagtcc tgagcaacag tgcagaggtg aaacgggagc gcctggaaga 240
tgtggtggga ggctgttgct atcgggtcaa caacagcttg gaccatgagt accaaccacg 300
gcccgtggag gtgatcacca gttctgcgaa ggagatggtt ggtcagaaga tgaagtacag 360
tattgtgagc aggaactgtg agcactttgt cacccagacc t 401

<210> 197
<211> 471
<212> DNA
<213> Homo sapiens

<400> 197
ctgtaatgat gtgagcaggg agccttcctc cctgggccac ctgcagagag ctttcccacc 60
aactttgtac cttgattgcc ttacaaagtt atttgtttac aaacagcgac catataaaag 120
cctcctgccc caaagcttgt gggcacatgg gcacatacag actcacatac agacacacac 180
atatatgtac agacatgtac tctcacacac acaggcacca gcatacacac gtttttctag 240
gtacagctcc caggaacagc taggtgggaa agtcccatca ctgagggagc ctaaccatgt 300
ccctgaacaa aaattgggca ctcatctatt ccttttctct tgtgtcccta ctcattgaaa 360
ccaaactctg gaaaggaccc aatgtaccag tatttatacc tctagtgaag cacagagaga 420
ggaagagagc tgcttaaact cacacaacaa tgaactgcag acacagacct g 471

<210> 198
<211> 201
<212> DNA
<213> Homo sapiens

<400> 198
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aagcccagaa gtttagggaa aagctgcaag aaataaagac actcaaccag aaggaggctg 120
tggcctatgc agtcaactcc tggaccacta gtatttcagg tatgctgctg aaagtgggaa 180
tcctctacat tggtgggcag a 201

<210> 199
<211> 551
<212> DNA
<213> Homo sapiens

<400> 199
tctggcacag atcttcaccc acacggcggt ccacgtgctg atcatcttcc gggtctcacc 60
gggcctggaa cacaccatct tccccatgag cccggtgccc agtctggtga cttccatctt 120
ggcccctggc cttatgtccc agttatgacc cctgacttca actctggctc ttaccctgta 180
actccagtcc atctctgaca tttttaacac ccggccttgt gaccgtggac atagctcctg 240
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tccaaccttg tgatcctaat tctgggacct caatcctagc ctctgaactt gggaccctgg 360
agctcctgac cttagtcctg accgctaccc ttgattctga cctttgatcc tgtaacttag 420
gggtggcccc tgaccttatt actgtcattt agctccttga ccttgccact tcaatcctgg 480
ctttatgacc tcctactctc aattttaact ttaaccaaat gaccaaattt gtgacactaa 540
atgaccacaa t 551

<210> 200
<211> 211
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(211)
<223> n=A,T,C or G

<400> 200
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tgtaagagag gctgctgnca ccattacctg cagaaacctt ctcatagggg ctacgatcgg 120

tactgctagg gggcacatag cgcccatggg tgtggtaggt ggggnactcn ntnataggat 180
ggtaggtatc ccgggctgga aanatgnnca g 211

<210> 201
<211> 111
<212> DNA
<213> Homo sapiens

<400> 201
ccagtgaaag gaaacaaaac tggcagtttg tccatttgaa tatcagacct agtttcttct 60
taatttccac actatttctc ccatattcct taaacttctt ggcatccacc t 111

<210> 202
<211> 331
<212> DNA
<213> Homo sapiens

<400> 202
tgaaaatаca gaataccagg tggtcccaaa tgtttgaagt tctttgaaca gaaagagaga 60
ggagagagag agagaggaaa attccctaac ccttggttta aagacaatat tcatttattg 120
ctcaaatgat gcttttaagg gaggacagtg gaataaaata aacttttttt ttctccctac 180
aatacataga agggttatca aaccactcaa gtttcaaaat ctttccaggg tccaatatca 240
ctttttttct ttcggttcaa tgaaaagcta aatgtaataa tactaattat agataaaatt 300
ttattttact ttttaaaaat ttgtccagac c 331

<210> 203
<211> 491
<212> DNA
<213> Homo sapiens

<400> 203
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ggctttagtg taaccaataa atctgtagtg accttacctg tattccctgt gctatcctgt 120
gggaaggtag gaatgggcta agtatgatga atgtataggt tagggatctt ttggttttaa 180
atcacagaaa acctaattca aactggctta aaataaaaag gatttattgg ttcatgtaac 240
tagaaagtcc ataggtagtg ctggctccag gtgaagactt gacccagtag ttcagtatgt 300
ctctaaatac cggactgact tttttctcac tgttgcatct tctgtaggac catttaagtc 360
tgggccactt aatggctgcc agcattccta agattacact tttccccatt tatgtccaat 420
cagaaaaaga aggcatcttt gtaccagaaa tctcagcaaa agccctaata ttcacactga 480
ttaggacctg c 491

<210> 204
<211> 361
<212> DNA
<213> Homo sapiens

<400> 204
tcccttcctc ccccatgtga taaatgggtc cagggctgat caaagaactc tgactgcaga 60
actgccgctc tcagtggaca gggcatctgt tatcctgaga cctgtggcag acacgtcttg 120
ttttcatttg atttttgtta agagtgcagt attgcagagt ctagaggaat ttttgtttcc 180
ttgattaaca tgattttcct ggttgttaca tccagggcat ggcagtggcc tcagccttaa 240
actttgttc ctactcccac cctcagcgaa ctgggcagca cggggagggt ttggctaccc 300
ctgcccatcc ctgagccagg taccaccatt gtaaggaaac actttcagaa attcagacct 360
c 361

<210> 205
<211> 471
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> (2)
<223> n=A,T,C or G
<221> misc_feature
<222> (3)
<223> n=A,T,C or G

<400> 205
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ctctgaaacc agagctcctc ctccctcccc gggcagggtg gagctgagaa gggctgctct 120
agcgttggga ctccacctcc atacacctga tattttgata gggcaggtcc ctgctatggg 180
ccactgttct gggcagtata gtatgcttga cagcatcctt ggcatctatc caccagatcc 240
cagagcaccc gctactagct gtgacaacat cctccaaaca ttgcaaaatt tcccctggga 300
ggcaagattg cctcagatgg gagaatcacg ctctagggaa atctgctggt atgagaaccc 360
caactcccca ctccactgag cctccagatg gcgagcaggc tgcagctcca gcacagacac 420
gaagctccct ccagccactg acggtccatg gctggggtta cccaggacct c 471

<210> 206
<211> 261
<212> DNA
<213> Homo sapiens

<400> 206
tagagtattt agagtcctga gataacaagg aatccaggca tcctttagac agtcttctgt 60
tgtcctttct tcccaatcag agatttgtgg atgtgtggaa tgacaccacc accagcaatt 120
gtagccttga tgagagaatc caattcttca tctccacgaa tagcaagttg caagtgacga 180
ggggtaatac gctttacctt taagtctttt gatgcatttc ctgccagttc aagtacctct 240
gcggtgaggt actccaggat g 261

<210> 207
<211> 361
<212> DNA
<213> Homo sapiens

<400> 207
gctctccggg agcttgaaga agaaactggc tacaaagggg acattgccga atgttctcca 60
gcggtctgta tggacccagg cttgtcaaac tgtactatac acatcgtgac agtcaccatt 120
aacggagatg atgccgaaaa cgcaaggccg aagccaaagc caggggatgg agagtttgtg 180
gaagtcattt ctttacccaa gaatgacctg ctgcagagac ttgatgctct ggtagctgaa 240
gaacatctca cagtggacgc cagggtctat tcctacgctc tagcactgaa acatgcaaat 300
gcaaagccat ttgaagtgcc cttcttgaaa ttttaagccc aaatatgaca ctggacctgc 360
c 361

<210> 208
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(381)
<223> n=A,T,C or G

<400> 208
agaggagatn tttgccatgc ctgaatnctt tcctatncca ccctancact taacatatta 60
cttagtctgc tttgntaaaa gcaagtatta ccttnaactt gnctcttact ctttgccctt 120
tagctaacta ataaagnttg atntaggcat tattatataa ttctgagtca ttcatggtat 180
ctctcatgtt tgatgtattt tncaaactaa gatctatgat agttttttt ccanagttcc 240
attaaatcat ttatttcctt tactttctca cctctgtnga aacatttaga aactggattt 300
gggaacccan ttttggaaaa ccagattcat agtcatgaaa atggaaactt ncatattctg 360
tttttgaaaa gatgtggacc t 381

<210> 209

<211> 231
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (83)
<223> n=A,T,C or G

<400> 209
gtggagagca agtgatttat taaagcaaga cgttgaaacc tttacattct gcagtgaaga 60
tcagggtgtc attgaaagac agnggaaacc aggatgaaag tttttacatg tcacacacta 120
catttcttca atattttcac caggacttcc gcaatgaggc ttcgtttctg aagggacatc 180
tgatccgtgc atctcttcac tcctaacttg gctgcaacag cttccacctg c 231

<210> 210
<211> 371
<212> DNA
<213> Homo sapiens

<400> 210
tccatcctgg ttttgcagag atcaggttgt tgacagttcc tggttgaccc acagctaccc 60
atgtcagtta tctccactaa catatccaag aatctttgta ggacaatttc tccacctgca 120
aggtttttta ggtagaactc ttcttttaag gcaattagcc cattgccaaa aggttttact 180
gtcttaaagc tgtctttctg agatctaatt ccaaggactt ctccacagct aagtgagatg 240
cctcacacca ttaggtgatg ctttggacag aacagagtat tttcatcttg tgtttaaagc 300
aattccttgg cttcggctcc tcaccacttt ctatgccagt ctcccattta tgtccctagt 360
aatgcctatg c 371

<210> 211
<211> 471
<212> DNA
<213> Homo sapiens

<400> 211
tttattttaa aagaaaaaaa ttaaaataga gccaacaaat gcaattaaga aaaaaaaagt 60
attgagacac aaggggacct acatgttctg gtctaagaag catgcaagta ttacaaagca 120
ttccagatac agtatgacag aggaacagtg aacaagcatt ggaacgatgc tctttctttc 180
agaaacggga agtctaacag ttatgttttc acaatggtag tgattaaacc atctttattt 240
ttaaggaatt ttataggaag aattttagca ccatcattaa aggaaaaata ataatacctt 300
tttagccctg cctatctcca gtcttggaat aataacagaa gcatagcacc tttcagtatc 360
taaaatataa acaagaatag taagtccatc ccagcttcta gagatgaggt agctcatgct 420
aagaaatgtt gggtcatttt tcctatgaaa gttcaaaggc caaatggtca c 471

<210> 212
<211> 401
<212> DNA
<213> Homo sapiens

<400> 212
tggcctgtct ccttcacata gtccatatca ccacaaatca cacaacaaaa gggagaggat 60
atattttggg ttcaaaaaaa gtaaaaagat aatgtagctg catttctttg gttattttgg 120
gccccaaata tttcctcatc tttttgttgt tgtcatggat ggtggtgaca tggacttgtt 180
tatagaggac aggtcagctc tctggctcgg tgatctacat tctgaagttg tctgaaaatg 240
tcttcatgat taaattcagc ctaaacgttt tgccgggaac actgcagaga caatgctgtg 300
agtttccaac ctcagcccat ctgcgggcag agaaggtcta gtttgtccat caccattatg 360
atatcaggac tggttacttg gttaaggagg ggtctacctc g 401

<210> 213
<211> 461
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(461)
<223> n=A,T,C or G

<400> 213
tgtgaagcat acataaataa atgaagtaag ccatactgat ttaatttatt ggatgttatt 60
ttccctaaga cctgaaaatg aacatagtat gctagttatt tttcagtgtt agccttttac 120
tttcctcaca caatttggaa tcatataata taggtacttt gtccctgatt aaataatgtg 180
acggatagaa tgcatcaagt gtttattatg aaaagagtgg aaaagtatat agcttttanc 240
aaaaggtgtt tgcccattct aagaaatgag cgaatatata gaaatagtgn gggcatttct 300
tcctgttagg tggagtgtat gtgttgacat ttctccccat ctcttcccac tctgtttnnt 360
ccccattatt tgaataaagt gactgctgaa nangactttg aatccttatc cacttaattt 420
aatgtttaaa gaaaaaccta taatggaaag tgagactcct t 461

<210> 214
<211> 181
<212> DNA
<213> Homo sapiens

<400> 214
cctgagcttc tactcctttc ccttaagatt cctccaaagc accagctcca taaaatcctt 60
cagctcccca gacccacacc aagaacccca catgttaatt ggatcagcca aatctacaag 120
cagataagtc ctaaggagaa tgccgaagcg tttttcttct tcctcaagcc tagcatgaga 180
c 181

<210> 215
<211> 581
<212> DNA
<213> Homo sapiens

<400> 215
ctgctttaag aatggttttc cacctttcc ccctaatctc taccaatcag acacatttta 60
ttatttaaat ctgcacctct ctctatttta tttgccaggg gcacgatgtg acatatctgc 120
agtcccagca cagtgggaca aaaagaattt agaccccaaa agtgtcctcg gcatggatct 180
tgaacagaac cagtatctgt catggaactg aacattcatc gatggtctcc atgtattcat 240
ttattcactt gttcattcaa gtatttattg aatacctgcc tcaagctaga gagaaaagag 300
agtgcgcttt ggaaatttat tccagttttc agcctacagc agattatcag ctcggtgact 360
tttctttctg ccaccattta ggtgatggtg tttgattcag agatggctga atttctattc 420
ttagcttatt gtgactgttt cagatctagt ttgggaacag attagaggcc attgtcctct 480
gtcctgatca ggtggcctgg ctgtttcttt ggatccctct gtcccagagc cacccagaac 540
cctgactctt gagaatcaag aaaacaccca gaaaggacct c 581

<210> 216
<211> 281
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(281)
<223> n=A,T,C or G

<400> 216
ccgatgtcct gcttctgtgg accaggggct cctctgnngg tggcctcaac cacggctgag 60
atccctagaa gtccaggagc tgtggggaag agaagcactt agggccagcc agccgggcac 120
ccccacttgc gccccgaccc acgctcacgc accagacctg cccnggcggt cgctcnaaag 180
ggcgaattct gcagatatcc atcacactgg cggacgctcg agcatgcatc tagagggccc 240
aattcaccct atantgagtc gtattacaat tcactggccg t 281

<210> 217

<211> 356
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(356)
<223> n=A,T,C or G

<400> 217
atagcaggtt tcaacaattg tcttgtagtt tgnagtaaaa agacataaga aagagaaggt 60
gtggtttgca gcaatccgta gttggtttct caccataccc tgcagttctg tgagccaaag 120
gtcttgcaga aagttaaaat aaatcacaaa gactgctgtc atatattaat tgcataaaca 180
cctcaacatt gctcagagtt tcatccgttt ggttaagaaa acattccttc aattcatcta 240
tggcatttgt agtggcattg tcgtctatga actcttgaag aagttctttg tattcagtct 300
tagacacttg tggattgatt gncttggaaa tcacattctc caataaggga cctcgg 356

<210> 218
<211> 321
<212> DNA
<213> Homo sapiens

<400> 218
ttgtccatcg ggagaaaggt gtttgtcagt tgtttcataa accagattga ggaggacaaa 60
ctgctctgcc aatttctgga tttctttatt ttcagcaaac actttcttta aagcttgact 120
gtgtgggcac tcatccaagt gatgaataat catcaagggt ttgttgcttg tcttggattt 180
atatagagct tcttcatatg tctgagtcca gatgagttgg tcaccccaac ctctggagag 240
ggtctggggc agtttgggtc gagagtcctt tgtgtccttt ttggctccag gtttgactgt 300
ggtatctctg gacctgcctg g 321

<210> 219
<211> 271
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (41)
<223> n=A,T,C or G

<400> 219
ccggttaggt ccacgcgggg gcagtggagg cacaggctca nggtggccgg gctacctggc 60
accctatggc ttacaaagta gagttggccc agtttccttc cacctgaggg gagcactctg 120
actcctaaca gtcttccttg ccctgccatc atctggggtg gctggctgtc aagaaaggcc 180
gggcatgctt tctaaacaca gccacaggag gcttgtaggg catcttccag gtggggaaac 240
agtcttagat aagtaaggtg acttgtctaa g 271

<210> 220
<211> 351
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(351)
<223> n=A,T,C or G

<400> 220
gtcctacgac gaggaccagc ttttcttctt cnacttttcc canaacactc gggtgcctcg 60
cctgcccgaa tttgctgact gggctcagga acagggagat gctcctgcca ttttatttga 120
caaagagttc tgcgagtgga tgatccagca aatagggcca aaacttgatg ggaaaatccc 180
ggtgtccaga gggtttccta tcgctgaagt gttcacgctg aagcccctgg agtttggcaa 240

gcccaacact ttggtctgtt ttgtcagtaa tctcttccca cccatgctga cagtgaactg 300
gtagcatcat tccgtccctg tggaaggatt tgggcctact tttgtctcag a 351

<210> 221
<211> 371
<212> DNA
<213> Homo sapiens

<400> 221
gtctgcagaa gcgtgtctga ggtgtccggt ggaggtggca gccgagctct gggactaatc 60
accgtgctgg ggacggcacc gcgtcaggat gcaggcagat ccctgcagaa gtgtctaaaa 120
ttcacactcc tcttctggag ggacgtcgat ggtattagga tagaagcacc aggggacccc 180
acgaacggtg tcgtcgaaac agcagccctt atttgcacac tgggagggcg tgacaccagg 240
aaaaccacaa ttctgtcttt cacgggggc cactgtacac gtctctgtct gggcctcggc 300
cagggtgccg agggccagca tggacaccag gaccagggcg cagatcacct tgttctccat 360
ggtggacctc g 371

<210> 222
<211> 471
<212> DNA
<213> Homo sapiens

<400> 222
gtccatgttc catcattaat gttccaacat caccagggac acaaagctgc aaaaatgaga 60
agggaaataa ggttagagaa aggatccggg caatcttaag gactgaggaa gacatgttcc 120
ccaacccttg aactcacaaa ccctgaagct caaggattgc atccttcctc caaatctcac 180
tcaacataat aagtgcagaa caacatgcca aagcactgta tgaagcacta gggacaaaga 240
caaggtcaaa atccttgtaa ccaaatttaa tggtattgta atgcagtgtt aacacaggac 300
agtaacagaa cacccaagaa ccaaacagaa gagggtaggg ataagcataa atgaagtaac 360
atgaaataaa cttccaaatg gaaaacttgt ccatacccc agggcaagtc aactacagtc 420
tcccaaagga cataaattcc acttagggca cactagacag aaaacaatat t 471

<210> 223
<211> 411
<212> DNA
<213> Homo sapiens

<400> 223
agttgctcta caatgacaca caaatcccgt taaataaatt ataaacaagg gtcaattcaa 60
atttgaagta atgttttagt aaggagagat tagaagacaa caggcatagc aaatgacata 120
agctaccgat taactaatcg gaacatgtaa aacagttaca aaaataaacg aactctcctc 180
ttgtcctaca atgaaagccc tcatgtgcag tagagatgca gtttcatcaa agaacaaaca 240
tccttgcaaa tgggtgtgac gcggttccag atgtggattt ggcaaaacct catttaagta 300
aaaggttagc agagcaaagt gcggtgcttt agctgctgct tgtgccgctg tggcgtcggg 360
gaggctcctg cctgagcttc cttccccagc tttgctgcct gagaggaacc a 411

<210> 224
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (31)
<223> n=A,T,C or G

<400> 224
ggtctgaagt ttgataacaa agaaatatat ntaagacaaa aatagacaag agttaacaat 60
aaaaacacaa ctatctgttg acataacata tggaaacttt ttgtcagaaa gctacatctt 120
cttaatctga ttgtccaaat cattaaaata tggatgattc agtgccattt tgccagaaat 180
tcgtttggct ggatcataga ttaacatttt cgagagcaaa tccaagccat tttcatccaa 240
gtttttgaca tgggatgcta ggcttcctgg tttccatttg ggaaatgtat tcttatagtc 300

ctgtaaagat tccacttctg g 321

<210> 225
<211> 251
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (34)
<223> n=A,T,C or G

<400> 225
atgtctgggg aaagagttca ttggcaaaag tgtnctccca agaatggttt acaccaagca 60
gagaggacat gtcactgaat ggggaaaggg aacccccgta tccacagtca ctgtaagcat 120
ccagtaggca ggaagatggc tttgggcagt ggctggatga aagcagattt gagataccca 180
gctccggaac gaggtcatct tctacaggtt cttccttcac tgagacaatg aattcagggt 240
gatcattctc t 251

<210> 226
<211> 331
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (1)...(331)
<223> n=A,T,C or G

<400> 226
gttaggtccc aggccccccg ccaagnggtt accnnnntna ccactcctga cccaaaaatc 60
aggcatggca ttaaaacgtt gcaaattcct ttactgttat ccccccccacc accaggacca 120
tgtagggtgc agtctttact ccctaacccg tttcccgaaa aaggtgctac ctcctttcca 180
gacagatgag agagggcagg acttcaggct ggatccacca ctgggctctc cctcccccag 240
cctggagcac gggaggggag gtgacggctg gtgactgatg gatgggtagt gggctgagaa 300
gaggggacta ggaagggcta ttccaggctc a 331

<210> 227
<211> 391
<212> DNA
<213> Homo sapiens

<400> 227
aggtctgccc ttgaagtata ggaaggaatc atagttggag gacttctgca ttatttgttg 60
gctgaagcta gaagtgcaac cccctcctga tttctgcagc aagatgaact gccttatccc 120
cagcccgcag gaatgttcat atctgagcaa tcaatgggca ctgtgttcaa ccacgccatt 180
ttcaagattg gctccttaaa ccacccacaa ggcaccagct ctgggagaag ctgcagggag 240
aagagaacaa agccctcgct gtgatcagga tgggtgtctc atacctttc tctggggtca 300
ttccaggtat gagacagagt tgaacctgcg catgagcgtg gaggccgaca tcaacggcct 360
gcgcagggtg ctggatgagc tgaccctgga c 391

<210> 228
<211> 391
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (35)
<223> n=A,T,C or G

<400> 228

gttgtccata gccacctcct gggatagaag ctttntagtt catagttcga ttagtgtgtc 60
cttaggacat aggtccagcc ctacagatta gctgggtgaa gaaggcaagt gtctcgacag 120
ggcttagtct ccaccctcag gcatggaacc attcagggtg aagcctggga tgtgggcaca 180
ggagactcag gctgatataa aaataacaaa atcagtaata aaaaaattat aaaacctgtt 240
gcttgtctga atagatttga gcaacagtct tgcttttgtt aaaatcctgg agccgttaag 300
tcctgaatat tcttctggac atcattgctg gctggagaaa ggagccccag gcccggctcg 360
gctgacatct gtcaggtttg gaagtctcat c 391

<210> 229
<211> 341
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (202)
<223> n=A,T,C or G

<400> 229
gtccatggct tctcacccag acagtctttc tgggcaactt ggggaagccc ctgttctgct 60
caagtctcac cccatggaag aggtggggga agggggcctt ggtttttcag gaagacgggt 120
tggagagcac gagtcactac aaagcagtaa aagtgaatgg tgtctccagg ggctgggtcc 180
agaacaccgc ggagagcccc anccataaag gtgtgttccg cctctggcct gcaggaatct 240
ctttgaatct ctttgattgg tggctccaag agcaatggga agtcaacagc caggaggctg 300
gactgggttc cctgggaccc cgaggtccca gaggctgctg g 341

<210> 230
<211> 511
<212> DNA
<213> Homo sapiens

<400> 230
gtccaagcca aggaaaccat tcccttacag gagacctccc tgtacacaca ggaccgcctg 60
gggctaaagg aaatggacaa tgcaggacag ctagtgtttc tggctacaga aggggaccat 120
cttcagttgt ctgaagaatg gttttatgcc cacatcatac cattccttgg atgaaacccg 180
tatagttcac aatagagctc agggagcccc taactcttcc aaaccacatg ggagacagtt 240
tccttcatgc ccaagcctga gctcagatcc agcttgcaac taatccttct atcatctaac 300
atgccctact tggaaagatc taagatctga atcttatcct ttgccatctt ctgttaccat 360
atggtgttga atgcaagttt aattaccatg gagattgttt tacaaacttt tgatgtggtc 420
aagttcagtt ttagaaaagg gagtctgttc cagatcagtg ccagaactgt gcccaggccc 480
aaaggagaca actaactaaa gtagtgagat a 511

<210> 231
<211> 311
<212> DNA
<213> Homo sapiens

<400> 231
ggtccaagta agctgtgggc aggcaagccc ttcggtcacc tgttggctac acagacccct 60
cccctcgtgt cagctcaggc agctcgaggc ccccgaccaa cacttgcagg ggtccctgct 120
agttagcgcc ccaccgccgt ggagttcgta ccgcttcctt agaacttcta cagaagccaa 180
gctccctgga gccctgttgg cagctctagc tttgcagtcg tgtaattggc ccaagtcatt 240
gtttttctcg cctcactttc caccaagtgt ctagagtcat gtgagcctcg tgtcatctcc 300
ggggtggacc t 311

<210> 232
<211> 351
<212> DNA
<213> Homo sapiens

<400> 232
tcgtttagct aataatccct tccttgatga tacactccaa cttcttgttt ttctttattt 60

ctaaaaagcg gttctgtaac tctcaatcca gagatgttaa aaatgtttct aggcacggta 120
ttagtaaatc aagtaaattt catgtcctct taaaggacaa acttccagag atttgaatat 180
aaatttttat atgtgttatt gattgtcgtg taacaaatgg cccccacaaa ttagtagctt 240
aaaatagcat ttatgatgtc actgttttct ttgccttttc attaatgttc tgtacagacc 300
tatgtaaaca acttttgtat atgcatatag gatagctttt ttgagggtat a 351

<210> 233
<211> 511
<212> DNA
<213> Homo sapiens

<400> 233
aggtctggat gtaaggatgg atgctctcta tacatgctgg gttggggatg ctgggactgc 60
acagccaccc ccagtatgcc gctccaggac tctgggacta gggcgccaaa gtgtgcaaat 120
gaaaatacag gatacccagg gaactttgaa tttcagattg tgaaaagaaa acaaatcttg 180
agactccaca atcaccaagc taaaggaaaa agtcaagctg ggaactgctt agggcaaagc 240
tgcctcccat tctattcaca gtcatccccc tgaggctcac ctgcatagct gattgcttcc 300
tttcccctat cgcttctgta aaaatgcaga ctcactgagc cagactaaat tgtgtgttca 360
gtggaaggct gatcaagaac tcaaaagaat gcaacctttt gtctcttatc tactacaacc 420
aggaagcccc cacttaaggg ttgtcccacc ttactggact gaaccaaggt acatcttaca 480
cctactgatt gatgtctcat gtccccctaa g 511

<210> 234
<211> 221
<212> DNA
<213> Homo sapiens

<400> 234
caggtccagc gaaggggctt cataggctac accaagcatg tccacataac cgaggaagct 60
ctctccatca gcatagcctc cgatgaccat ggtgttccac aaagggttca tcttcgagcg 120
ccggctgtac atggccctgg tcagccatga atgaatagct ctaggactat agctgtgtcc 180
atctcccaga agctcctcat caatcaccat ctggccgaga c 221

<210> 235
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (33)
<223> n=A,T,C or G

<400> 235
ggtccaagaa agggacatct atgtgaaagt ganactgaga cagtgctggt cacaggtcat 60
gctgcagaat aatacattcc caggcactgt cacgtggggg acccaagagg ccccaggagt 120
gacctataac ctctccagaa agaccactct gtgtggcatc acagtccaca cagtttaagg 180
aaatatttag acttaacaat cagacaccag ctcttactca cacttacact cacagcccac 240
acacaagtgt gcaaacatac acacacatat atatttcctg atacattcat ggaatatcag 300
agccctgccc tgaagtcgtt agtgtctctg ctccccaaac cgctgctccc acattggcta 360
agctccctca agagacctca g 381

<210> 236
<211> 441
<212> DNA
<213> Homo sapiens

<400> 236
aggtcctgtt gccccttttct tttgcccaac ttcgccattt gggaattgga atatttaccc 60
aacacctgta ctgcattgaa tattggaagc aaataacttg gctttgatct tataggctca 120
cagatggagg aacgtacctt gaagttcaga tgagatttcg gacttttgag ttgatgctga 180
aacagcttga gatttttggg gactactgag agatgataat tgtattgtgc aatatgagaa 240

ggacatgaga tttggtgggc ataggtgtga aatgacattg tttggatgtg tttaccctcc 300
aaatctcttg ttgaatgtga tcttaaacgt tggtggtggg cctagtggaa ggtgttgaat 360
catgggggtg gactcttcat aatttgctta gctccatccc cttggtgatg agcaagtcct 420
tgctctgttg tgtcacatga g 441

<210> 237
<211> 281
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(281)
<223> n=A,T,C or G

<400> 237
tcctaaaaaa ttagctgacc ttgttaaaaa tgttggcgtg agcagtatat tattacctat 60
ctttttttat tgtgtgtgtg ngtgtgtgtn ttaaactaat tggctgaaat atctgcctgt 120
ttccctcttt acatttttct tgtttctttc cttatttatc tttgtccatc ttgagatcta 180
ctgtaaagtg aatnttttaa tgaaaacann nccaagttnt actctcactg ggnttgggac 240
atcagatgta attgagaggc caacaggtaa gtcttcatgt c 281

<210> 238
<211> 141
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(141)
<223> n=A,T,C or G

<400> 238
gtctgcctcc tcctactgtt tccctctatn aaaaagcctc cttggcgcag gttccctgag 60
ctgtgggatt ctgcactggt gcttnggatt ccctgatatg ttccttcaaa tccactgaga 120
attaaataaa catcgctaaa g 141

<210> 239
<211> 501
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(501)
<223> n=A,T,C or G

<400> 239
aacaatctaa acaaatccct cggttctann atacaatgga ttccccatat tggaaggact 60
ctgangcttt attcccccac tatgcntatc ttatcatttt attattatac acacatccat 120
cctaaactat actaaagccc ttttcccatg catggatgga aatggaagat tttttttaa 180
cttgttctag aagtcttaat atgggctgtt gccatgaagg cttgcagaat tgagtccatt 240
ttctagctgc ctttattcac atagtgatgg ggtactaaaa gtactgggtt gactcagaga 300
gtcgctgtca ttctgtcatt gctgctactc taacactgag caacactctc ccagtggcag 360
atcccctgta tcattccaag aggagcattc atccctttgc tctaatgatc aggaatgatg 420
cttattagaa aacaaactgc ttgacccagg aacaagtggc ttagcttaag naaacttggc 480
tttgctcana tccctgatcc t 501

<210> 240
<211> 451
<212> DNA
<213> Homo sapiens

<400> 240
tgtcctgaaa ggccattact aatagaaaca cagcctttcc aatcctctgg aacatattct 60
gtctgggttt ttaatgtctg tggaaaaaaa ctaaacaagt ctctgtctca gttaagagaa 120
atctattggt ctgaaggttt ctgaacctct ttctggttct cagcagaagt aactgaagta 180
gatcaggaag gggctgcctc aggaaaattc ctagatccta ggaattcagt gagaccctgg 240
gaaggaccag catgctaatc agtgtcagtg aatccacagt ctttacttcc tgcctcataa 300
agggccaggt ctccccagta ccaagtcctt tcctcatgaa gttgtgttgc ctcaggctgt 360
ttagggacca ttgcctgtct tggtcacatg agtctgtctc cttactttag tccctgggca 420
atccttgctt aatgcttttg ttgactcaac g 451

<210> 241
<211> 411
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(411)
<223> n=A,T,C or G

<400> 241
aatctccagt gtgatggtat cggggttaga gcttcaatct ccagtgtgat ggtactgcag 60
cnagagcttc aatctccagt gngatggtat tagggttaga tcttcaatct ccagtgtgat 120
ggtatcaggg ttagagcttc agcctccagt gtgatggtat cagggttaga gcttcagcct 180
ccagtgtgat ggtatcgggg ttagatcttc aatccccagt ggtggtggtt agagcttcaa 240
tctccagtgt gatggtattg gggttagagc ttcaatctcc agtctgatgg tgtttcggga 300
tggggctttt aagatgtaat tagggtttaa gatcataagg gacctggtct gatggggatt 360
agtncgcttn tatgaagaga cacangaggg cttgctctat ctctgactct c 411

<210> 242
<211> 351
<212> DNA
<213> Homo sapiens

<400> 242
ttccccttca caacagtaga gacctacaca gtgaactttg gggacttctg agatcagcgt 60
cctaccaaga ccccagccca actcaagcta cagcagcagc acttcccaag cctgctgacc 120
acagtcacat cacccatcag cacatggaag gcccctggta tggacactga aaggaagggc 180
tggtcctgcc cctttgaggg ggtgcaaaca tgactgggac ctaagagcca gaggctgtgt 240
agaggctcct gctccacctg ccagtctcgt aagaaatggg gttgctgcag tgttggagta 300
ggggcagagg gagggagcca aggtcactcc aataaaacaa gctcatggca c 351

<210> 243
<211> 241
<212> DNA
<213> Homo sapiens

<400> 243
gtctgtgctt tatcaggaaa agcacaagaa tatgtttttc tacctaaaac cctcttctac 60
tttaaaaatg gtttgctgaa tttttctatg tttttaaaat gtttttatgc tttttttaa 120
acacgtaaag gatggaacct aatcctctcc cgagacgcct cctttgtgtt aatgcctatt 180
cttacaacag agaaacaagt acattaatat aaaaacgagt tgattattgg ggtataaaat 240
a 241

<210> 244
<211> 301
<212> DNA
<213> Homo sapiens

<400> 244
ggtccagagc aatagcgtct gtggtgaagc gcctgcactc ctcgggagac atgcctggct 60

tatatgctgc atccacataa ccatagataa aggtgctgcc ggagccacca atggcaaaag 120
gctgtcgagt cagcattcct cccagggttc catatacctg acctccttca cgttggtccc 180
agccagctac catgagatgt gcagacaagt cctctcgata tttatagctg atatttctca 240
ccacatttgc agcagccaaa acaagtggag gttcctccag ttctatccca tggagctcca 300
g 301

<210> 245
<211> 391
<212> DNA
<213> Homo sapiens

<400> 245
ctgacactgc tgatgtgggc cgggggggcgc cgaggcacaa ctggtggccg gaccattgag 60
gcacctggag ggtaggcagc ttgtggtgca gacaccacag agagagaaaa gttggatgga 120
gtggtgggaa taatcagggt ggcacactgt gcctagaagc ttccagggcc accaagagaa 180
tgggaaggga aactacaaca ttcacaacag aaataggagt caattcactt agacccagaa 240
ctccagaaag ggggagtgta ggaatctaca atttcaaagc cagctcgtgt ctacctagag 300
ccccaaactg cataagcacc aggattgtac accttagtcc ctcaagatag tttcaagtga 360
gcgtgcaatt cactcttaca gaggagggcc t 391

<210> 246
<211> 291
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(291)
<223> n=A,T,C or G

<400> 246
tcctccacag gggaagcagg aagttngacc agcttcaggc tggaacgtgc ccagggcaca 60
gagctggcaa ggtgcaaagn cntctgcaga atattcacca ggttgacaca gacctccaca 120
ttcagacata ttccaagctt ctggggtctt cagggcccca gaatttcctg gtcttgggca 180
tggtncacaa gtcatttgtc cttcctcatt ttggaaggtt ccatttggac ataaaatgca 240
agcgttctcg tgctncatna taataggtcc cagcctgcac tgacacattt g 291

<210> 247
<211> 471
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(471)
<223> n=A,T,C or G

<400> 247
cactgagtga atgagtatat aatttatgaa aacagaaaag tgctttggaa aaaaaaaaag 60
acaacaggag tacatacagn gaaccaaaaa gagtgtacca ggaggagcan accctgaaca 120
gttanaacta tggaaatcgc tatgctttgt gttgtcacag gagttaaaat aggaataccc 180
tgcatacaat aaatatttat tggataaata actaagcctg ataccctttt caatgcgtta 240
tacanactnt atcatcacac cactaatcta agttctcana agttaaacat tacaagactt 300
cagaacaaca taggcgtntt tggctccatt taacanaana aggaccatag tgatcattta 360
atctctatga gtctgtctta tcttctggaa aaggggccta acaccatttc cttttgcaaa 420
aaggtagctg ccttgcttcc agttctacca tcctntagca acccatcttt n 471

<210> 248
<211> 551
<212> DNA
<213> Homo sapiens

<400> 248
ccatgggatc aggaatgggg tcaggtcagt tgacctgagc atacccatta aacatgttca 60
aatgtcccca tcccacccac tcacatgaca tggctcccga gccctgagat ctgtatccca 120
agaacctcag ttgagaaata tttatggcag cttcactgtt gctcaagagc ctgggtattg 180
tagcagcctg ggggcaggtt gtccctaatg ttctccaagt tcttcacatc agccagaatc 240
ccatctatgc ttgtctccag caaatggagg tggcccctct gctgacgtgc cctctcttcc 300
agctctgaca tcatgggccg cagttggctg ttgatctggg tcttggctcg ggaaagcttc 360
tgctccagta agaccagccc ctcttcatct acactgagag gctggtccat cagatgcagg 420
aggccgtcta atgtgttgag tgtgtcttgg attgtaaccc cagcgttctt ggctctggta 480
tcaaccttct gggcttctgt aatcaccatc tgtactgcat ccatattcgt gtcgaactcc 540
agctccttcc t 551

<210> 249
<211> 181
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(181)
<223> n=A,T,C or G

<400> 249
atntccagag ggaccgtaag actggtacaa gtttacacca taagaggcga cgtggtcagc 60
cacaatgtct tcacctccac aggggctcat cacggnggtc agggcaaggg cccccagcat 120
cagagctttg tttaggatca tcctcttccc aaggcagcct tagcagttgc tgacctgccc 180
g 181

<210> 250
<211> 551
<212> DNA
<213> Homo sapiens

<400> 250
tctgtagcta ggatgagctg gctctcaagc aaaagtttgt cttcctgggt ccatttgtgg 60
ttatcacttg ttattgaatg tacatcacaa attaaagtct gcattgttgg acgtaagaga 120
atgtgccgac tttggtaacc aggagatttc atgttactgg actgcctgta gtcacgtatt 180
tctgctatga cacatccgca atgaaaaata ttaacctgag atttttctag gagatcaacc 240
aaaataggag gtaattcttc tgcatccaaa tattcaagca actctccttc ttcatagggc 300
agtcgaatgg tctcggaatc tgatccgttt tttcccctga gcatcagaga atatccctca 360
tttcctgggt atagattgac cactaaacat gacaaagtct cttgcataac aagcttctct 420
aacaagttca catttcttct taatttctta acttcaggtt cttttcaca ttcttcaata 480
tacaagtcat aaagtttttg aaatacagat tttcttccac ttgataggta tttccttta 540
ggaggtctct g 551

<210> 251
<211> 441
<212> DNA
<213> Homo sapiens

<400> 251
tgtctgctct cccatcctgg ttactatgag tcgctcttgg cagaaaggac cacagatgga 60
gagcttggca ctcgctccaa ctttgccgaa aagaggacaa ccaccaaagt agtaggtaaa 120
aacacaattt tagcagcagt gaaataaaaa gaggaagtga ggatggggcc aggccgcaac 180
tataattaaa ctgtctgttt aggagaagct gaatccagaa gaaacacaag ctgtaaagtg 240
agagaggaca gggagcaggg cctttggaga gcaggagagg acaggctgtc accaagcgct 300
gctcggactc tgccctgaaa gatttgaatt ggacactgtc cagtcacgtg tgtggcaaac 360
cgtactccaa gcacttttct cacggcagag gaaggagctg ccatggctgt acccctgaac 420
gtttgtgggg ccagcgatgt g 441

<210> 252
<211> 406

<212> DNA
<213> Homo sapiens

<400> 252
tttttttttg aacaagtaaa aatttcttta tttgctgaca ataagataac ctacagggaa 60
aacctgatga aatctattaa aaagttacta aaactaataa aagaatttag gaaggttata 120
gaatgtaaga ccaagacaca aaaatcaatt acatttctat ataatagcaa tgaacagata 180
ctgaaatttt aaaaactaaa tcattttaca aaagtatcac aatatgaaac actccgggat 240
aaattggata aaagatgtgc aagactgtac aaaagctaca aaacatttat gaaggaaatt 300
ggaagataga aacaagatag aaaatgaaaa tattgtcaag agtttcagat agaaaatgaa 360
aaacaagcta agacaagtat tggagaagta tagaagatag aaaaat 406

<210> 253
<211> 544
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (224)
<223> n=A,T,C or G

<400> 253
gaaggagttc agtagcaaag tcacacctgt ccaattccct gagctttgct cactcagcta 60
atgggatggc aaaggtggtg gtgctttcat cttcaggcag aagcctctgc ccatcccccc 120
caagggctgc aggcccagtt ctcatgctgc ccttgggtgg gcatctgtta acagaggaga 180
acgtctgggt ggcggcagca gctttgctct gagtgcctac aaanctaatg cttggtgcta 240
gaaacatcat cattattaaa cttcagaaaa gcagcagcca tgttcagtca ggctcatgct 300
gcctcactgc ttaagtgcct gcaggagccg cctgccaagc tccccttcct acacctggca 360
cactggggtc tgcacaaggc tttgtcaacc aaagacagct tccccctttt gattgcctgt 420
agactttgga gccaagaaac actctgtgtg actctacaca cacttcaggt ggtttgtgct 480
tcaaagtcat tgatgcaact tgaaaggaaa cagtttaatg gtggaaatga actaccattt 540
ataa 544

<210> 254
<211> 339
<212> DNA
<213> Homo sapiens

<400> 254
tggcattcag ggcagtgtct tctgcatctc ctaggaacct cgggagcggc agctccggcg 60
cctggtagcg agaggcgggt tccggagatc ccggcctcac ttcgtcccac tgtggttagg 120
ggtgagtcct gcaaatgtta agtgatttgc tcaaggtgcc catttcgcag gaattggagc 180
ccaggccagt tctctgagcc tatcattagg gctaaaggag tgcgtgatca gaatggtgtc 240
tggacggttc tacttgtcct gcctgctgct ggggtccctg ggctctatgt gcatcctctt 300
cactatctac tggatgcagt actggcgtgg tggctttgc 339

<210> 255
<211> 405
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(405)
<223> n=A,T,C or G

<400> 255
gaggtttttt nttttttttt ttttttttt caattaaana tttgatttat tcaagtatgt 60
gaaaacattn tacaatggaa acttttntta aatgctgcat gtnctgtgct atggaccacn 120
cacatacagc catgctgttt caaaaaactt gaaatgccat tgatagttta aaaactntac 180
ncccgatgga aaatcgagga aaacaattta atgtttcatn tgaatccana ggngcatcaa 240

attaaatgac agctccactt ggcaaataat agctgttact tgatggtatc caaaaaaaaa 300
tggttgggga tggataaatt caaaaatgct tccccaaagg ngggnggttt ttaaaaagtt 360
tcaggncaca acccttgcan aaaacactga tgcccaacac antga 405

<210> 256
<211> 209
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (6)
<223> n=A,T,C or G

<400> 256
gggcangtct ggtcctctcc ccacatgtca cactctcctc agcctctccc ccaaccctgc 60
tctccctcct cccctgccct agcccaggga cagagtctag gaggagcctg gggcagagct 120
ggaggcagga agagagcact ggacagacag ctatggtttg gattggggaa gaggttagga 180
agtaggttct taaagaccct tttttagta 209

<210> 257
<211> 343
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(343)
<223> n=A,T,C or G

<400> 257
tctggacacc ataatccctt ttaagtggct ggatggtcac acctctccca ttgacaagct 60
gggttaagtc aataggttga ctaggatcaa cacgacccaa atcaataaga tactgcagtc 120
tattgagact caaaggctta tactggcgtc tgaaactatg tccttcgtta aacccgtatt 180
ttgggattcg gatgtaaaat ggagtctggc ctccctcaaa gcccaagcgg ggccgggttc 240
ctctttgcct ttctccttta tggcctctgc cacattttct acctcttctc cgacctcttg 300
gtcttntctc nggtttcttg gagccgggat tcggctttaa gtn 343

<210> 258
<211> 519
<212> DNA
<213> Homo sapiens

<400> 258
gcggcttctg acttctagaa gactaaggct ggtctgtgtt tgcttgtttg cccacctttg 60
gctgataccc agagaacctg ggcacttgct gcctgatgcc caccctgcc agtcattcct 120
ccattcaccc agcgggaggt gggatgtgag acagcccaca ttggaaaatc cagaaaaccg 180
ggaacaggga tttgcccttc acaattctac tccccagatc ctctcccctg gacacaggag 240
acccacaggg caggacccta agatctgggg aaaggaggtc ctgagaacct tgaggtaccc 300
ttagatcctt ttctacccac tttcctatgg aggattccaa gtcaccactt ctctcaccgg 360
cttctaccag ggtccaggac taaggcgttt tctccatagc ctcaacattt tgggaatctt 420
cccttaatca cccttgctcc tcctgggtgc ctggaagatg gactggcaga gacctctttg 480
ttgcgttttg tgctttgatg ccaggaatgc cgcctagtt 519

<210> 259
<211> 371
<212> DNA
<213> Homo sapiens

<400> 259
attgtcaact atatacacag tagtgaggaa taaaatgcac acaaaacaat ggatagaata 60
tgaaaatgtc ttctaaatat gaccagtcta gcatagaacc ttcttctctt ccttctcagg 120

tcttccagct ccatgtcatc taacccactt aacaaacgtg gacgtatcgc ttccagaggc 180
cgtcttaaca actccatttc caaaagtcat ctccagaaga catgtatttt ctatgatttc 240
ttttaaacaa atgagaattt acaagatgtg taactttcta actctatttt atcatacgtc 300
ggcaacctct ttccatctag aagggctaga tgtgacaaat gttttctatt aaaaggttgg 360
ggtggagttg a 371

<210> 260
<211> 430
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(430)
<223> n=A,T,C or G

<400> 260
ttggattttt tgacttgcga tttcagtttt tttacttttt ttttttttt ttttganaaa 60
tactatattt attgtcaaag agtggtacat aggtgagtgt tcatcttccc tctcatgccg 120
gtatactctg cttcgctgtt tcagtaaaag ttttccgtag ttctgaacgt cccttgacca 180
caccataana caagcgcaag tcactcanaa ttgccactgg aaaactggct caactatcat 240
ttgaggaaag actganaaag cctatcccaa agtaatggac atgcaccaac atcgcggtac 300
ctacatgttc ccgtttttct gccaatctac ctgtgtttcc aagataaatt accacccagg 360
gagtcacttc ctgctatgtg aacaaaaacc cggtttcttt ctggaggtgc ttgactactc 420
tctcgngagc 430

<210> 261
<211> 365
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (178)
<223> n=A,T,C or G

<400> 261
tcctgacgat agccatggct gtaccactta actatgattc tattccaact gttcagaatc 60
atatcacaaa atgacttgta cacagtagtt tacaacgact cccaagagag gaaaaaaaaa 120
aaaaaagacg cctcaaaatt cactcaactt ttgagacagc aatggcaata ggcagcanag 180
aagctatgct gcaactgagg gcacatatca ttgaagatgt cacaggagtt taagagacag 240
gctggaaaaa atctcatact aagcaaacag tagtatctca taccaagcaa aaccaagtag 300
tatctgctca gcctgccgct aacagatctc acaatcacca actgtgcttt aggactgtca 360
ccaaa 365

<210> 262
<211> 500
<212> DNA
<213> Homo sapiens

<400> 262
cctagatgtc atttgggacc cttcacaacc attttgaagc cctgtttgag tccctgggat 60
atgtgagctg tttctatgca taatggatat tcggggttaa caacagtccc ctgcttggct 120
tctattctga atccttttct ttcaccatgg ggtgcctgaa gggtggctga tgcatatggt 180
acaatggcac ccagtgtaaa gcagctacaa ttaggagtgg atgtgttctg tagcatccta 240
tttaaataag cctattttat cctttggccc gtcaactctg ttatctgctg cttgtactgg 300
tgcctgtact tttctgactc tcattgacca tattccacga ccatggttgt catccattac 360
ttgatcctac tttacatgtc tagtctgtgt ggttggtggt gaataggctt ctttttacat 420
ggtgctgcca gcccagctaa ttaatggtgc acgtggactt ttagcaagcg ggctcactgg 480
aagagactga acctggcatg 500

<210> 263

<211> 413
<212> DNA
<213> Homo sapiens

<400> 263
ctcagagagg ttgaaagatt tgcctacgaa agggacagtg atgaagctaa gctctagatc 60
caggatgtct gacttcaaat tgaaactccc aaagtaatga gtttggaagg gtggggtgtg 120
gcctttccag gatgggggtc ttttctgctc ccagcggata gtgaaacccc tgtctgcacc 180
tggttgggcg tgttgctttc ccaaaggttt ttttttagg tccgtcgctg tcttgtggat 240
taggcattat tatctttact ttgtctccaa ataacctgga gaatggagag agtagtgacc 300
agctcagggc cacagtgcga tgaggaccat cttctcacct ctctaaatgc aggaagaaac 360
gcagagtaac gtggaagtgg tccacaccta ccgccagcac attgtgaatg aca 413

<210> 264
<211> 524
<212> DNA
<213> Homo sapiens

<400> 264
tccaatgggg ccctgagagc tgtgacagga actcacactc tggcactggc agcaaaacac 60
cattccaccc cactcatcgt ctgtgcacct atgttcaaac tttctccaca gttccccaat 120
gaagaagact catttcataa gtttgtggct cctgaagaag tcctgccatt cacagaaggg 180
gacattctgg agaaggtcag cgtgcattgc cctgtgtttg actacgttcc cccagagctc 240
attaccctct ttatctccaa cattggtggg aatgcacctt cctacatcta ccgcctgatg 300
agtgaactct accatcctga tgatcatgtt ttatgaccga ccacacgtgt cctaagcaga 360
ttgcttaggc agatacagaa tgaagaggag acttgagtgt tgctgctgaa gcacatcctt 420
gcaatgtggg agtgcacagg agtccaccta aaaaaaaaaa tccttgatac tgttgcctgc 480
ctttttagtc accccgtaac aagggcacac atccaggact gtgt 524

<210> 265
<211> 344
<212> DNA
<213> Homo sapiens

<400> 265
tcctttcttc tacttcagga gatgattcaa agttacttgt ggacatttct ttaagttctg 60
aagacaaatg agacaggatt tggcctgcgg gttcttcaga cttctctacc acctccatta 120
actcttcatc ttggcttgac gtaggcaatg cactattttg ctcttttgtt tctggagatg 180
acccagcacc acttctttct cttggcgggg ttctaagtgt gtctttgaat accagtgaag 240
actcaggcct atcctgtact ggaaagggac taaatttgtc tttctgtcta ggaggtgatg 300
cagtagcatc ctcctgaggg ggtaaggcca ttttctcttt ttga 344

<210> 266
<211> 210
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (78)
<223> n=A,T,C or G

<400> 266
ccacaatgtc cataacttga gcaggctttg gcatcccacc accccttca gaccaataca 60
cactatgttg gaggaacnac tttaaaatgt aaaatgagaa atgggcactg aacactccat 120
cctcactccc aacagcccac ccacacacct cttcaactgc tatccaaaca tggaggagct 180
cttgtggaag agaggctcaa caccaaataa 210

<210> 267
<211> 238
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(238)
<223> n=A,T,C or G

<400> 267
tcggncctcc caccctctna ctgaaattct ntgaaattct ccccttgggg atgaggatgg 60
caaccccagg catgtaccct cccaacctgg gacccgacct aataccctaa catcctgctg 120
acagtggctg ttctcgctgg gcaggcgtcc caaagcacat cgagccagat tcaggcagag 180
tggaactggc ccctcagcca tcagtggagg tggcctggga ggctctaccc tgaacggg 238

<210> 268
<211> 461
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (459)
<223> n=A,T,C or G

<400> 268
tcctcaagga catgcccctt gatagaaact cagttcctgt ctccagttcc ctcctggacc 60
tgatccccca aatgcagggc ctgggactat atccagttcc ttattttcag aggcccatgc 120
acaagatgca cagcaaataa gtgctgaata aagacccagc tactgctagc ttaccctgct 180
ccaaacattc accaagtcct cagcaaagag ggccatccat tcacctcttc taaaaacaca 240
ctgagctccc cagtctatac cccaagatat gcttggctcc caactatccc tcctctctca 300
tctccaagcc agtttccccc ttctaagtat actgatatta ccaaagacac tgacaatctt 360
cttttcctac ctctccccag tgactaggtt tgcagcagga gctctataag tcctagtata 420
cagcagaagc tccataaatg tgtgctgacc taacattang c 461

<210> 269
<211> 434
<212> DNA
<213> Homo sapiens

<400> 269
ctgtgttggt gagcaccgat tcccactcaa tatggcgtgg cttacagtct tcattaggtt 60
cccgctccca accagaatga ggaatgatca cttcatctgt caaggcatgc agtgcatggt 120
ccacaatctc cattttgatt gagtcatggg atgaaagatt ccacagggtt ccggtaataa 180
cttcagtaag gtccatatca cgagcctttc gaagcaatcg cacaagggca ggcacaccat 240
cacagttttt tatggcaatc ttgttatcct ggtcacgtcc aaaagagata ttcttgagag 300
ctccacaggc tccaaggtgc acttcctttt tgggatggtc taacaatccc accagtactg 360
ggatgccctt gagcttccgc acgtcagtct tcaccttgtc attgcggtag cataagtgtt 420
gcaggtatgc aaga 434

<210> 270
<211> 156
<212> DNA
<213> Homo sapiens

<400> 270
ctgcaccagc gattaccagt ggcattcaaa tactgtgtga ctaaggattt tgtatgctcc 60
ccagtagaac cagaatcaga caggtatgag ctagtcaaca gcaagtcttt gttggattcg 120
agtaggctca ggatctgctg aaggtcggag gagtta 156

<210> 271
<211> 533
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(533)
<223> n=A,T,C or G

<400> 271
ccactgtcac ggtctgtctg acacttactg ccaaacgcat ggcaaggaaa aactgcttag 60
tgaagaactt agaagctgtg gagaccttgg ggtccacgtn caccatctgc tctgataaaa 120
ctggaactct gactcanaac cggatgacag tggcccacat gtggtttgac aatcaaatcc 180
atgaagctga tacgacagag aatcagagtg gtgtctcttt tgacaagact tcagctacct 240
ggcttgctct gtccagaatt gcaggtcttt gtaacagggc agtgtttcag gctaaccagg 300
aaaacctacc tattcttaag cgggcagttg caggagatgc ctctgagtca gcactcttaa 360
agtgcataga gctgtgctgt ggntncgtga aggagatgag agaaagatac nccaaaatcg 420
tcgagatacc cttcaactcc accaacaagt accagttgtc tattcataag aaccccaaca 480
catcggagcc ccaacacctg ttggtgatga agggcgcccc agaaaggatc cta 533

<210> 272
<211> 630
<212> DNA
<213> Homo sapiens

<400> 272
tggtattttt ctttttcttt tggatgtttt atacttttt ttctttttc ttctctattc 60
ttttcttcgc cttcccgtac ttctgtcttc cagttttcca cttcaaactt ctatcttctc 120
caaattgttt catcctacca ctcccaatta atctttccat tttcgtctgc gtttagtaaa 180
tgcgttaact aggctttaaa tgacgcaatt ctccctgcgt catggatttc aaggtctttt 240
aatcaccttc ggtttaatct ctttttaaaa gatcgccttc aaattatttt aatcacctac 300
aacttttaaa ctaaacttta agctgtttaa gtcaccttca ttttaatcta aaagcattgc 360
ccttctattg gtattaattc ggggctctgt agtcctttct ctcaattttc ttttaaatac 420
atttttact ccatgaagaa gcttcatctc aacctccgtc atgttttaga aacctttat 480
cttttccttc ctcatgctac tcttctaagt cttcatattt tctcttaaaa tcttaagcta 540
ttaaaattac gttaaaaact taacgctaag caatatctta gtaacctatt gactatattt 600
tttaagtagt tgtattaatc tctatctttc 630

<210> 273
<211> 400
<212> DNA
<213> Homo sapiens

<400> 273
tctggtttgc cctccagttc attctgaatc tagacttgct cagcctaatc aagttcctgt 60
acaaccagaa gcgacacagg ttcctttggt atcatccaca agtgaggggt acacagcatc 120
tcaacccttg taccagcctt ctcatgctac agagcaacga ccacagaagg aaccaattga 180
tcagattcag gcaacaatct ctttaaatac agaccagact acagcatcat catcccttcc 240
tgctgcgtct cagcctcaag tatttcaggc tgggacaagc aaacctttac atagcagtgg 300
aatcaatgta aatgcagctc cattccaatc catgcaaacg gtgttcaata tgaatgcccc 360
agttcctcct gttaatgaac cagaaacttt aaaacagcaa 400

<210> 274
<211> 351
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (2)
<223> n=A,T,C or G

<400> 274
tntgagtatg tcccagagaa ggtgaagaaa gcggaaaaga aattagaaga gaatccatat 60
gaccttgatg cttggagcat tctcattcga gaggcacaga atcaacctat agacaaagca 120
cggaagactt atgaacgcct tgttgcccag ttccccagtt ctggcagatt ctggaaactg 180

tacattgaag cagaggttac tattttattt tatttttttct tatatcagta ttgcagcatt 240
cactgtagtg atagaaaaca agttaggaac atagccaatt aggacaagga ggatttaaat 300
gtgtcttacc tttatttttgt aaaataggta taaaggagta attaaaatga a 351

<210> 275
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(381)
<223> n=A,T,C or G

<400> 275
gcgnggtcgc nnncgaggtc tgagaagccc ataccactat ttgttgagaa atgtgtggaa 60
tttattgaag atacagggtt atgtaccgaa ggactctacc gtgtcagcgg gaataaaact 120
gaccaagaca atattcaaaa gcagtttgat caagatcata atatcaatct agtgtcaatg 180
gaagtaacag taaatgctgt agctggagcc cttaaagctt tctttgcaga tctgccagat 240
cctttaattc catattctct tcatccagaa ctattggaag cagcaaaaat cccggataaa 300
acagaacgtc ttcatgcctt gaaagaaatt gttaagaaat ttcatcctgt aaactatgat 360
gtattcagat acgtgataac a 381

<210> 276
<211> 390
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (5)
<223> n=A,T,C or G

<400> 276
gctcngactc cggcgggacc tgctcggagg aatggcgccg ccgggttcaa gcactgtctt 60
cctgttggcc ctgacaatca tagccagcac ctgggctctg acgcccactc actacctcac 120
caagcatgac gtggagagac taaaagcctc gctggatcgc cctttcacaa atttggaatc 180
tgccttctac tccatcgtgg gactcagcag ccttggtgct caggtgccag atgcaaagaa 240
agcatgtacc tacatcagat ctaaccttga tcccagcaat gtggattccc tcttctacgc 300
tgcccaggcc agccaggccc tctcaggatg tgagatctct atttcaaatg agaccaaaga 360
tctgcttctg gcagacctcg gccgcgacca 390

<210> 277
<211> 378
<212> DNA
<213> Homo sapiens

<400> 277
tgggaacttc tggggtagga cgttgtctgc tatctccagt tccacagacc caaccagtta 60
cgatggtttt ggaccattta tgccgggatt cgacatcatt ccctataatg atctgcccgc 120
actggagcgt gctcttcagg atccaaatgt ggctgcgttc atggtagaac caattcaggg 180
tgaagcaggc gttgttgttc cggatccagg ttacctaatg ggagtgcgag agctctgcac 240
caggcaccag gttctcttta ttgctgatga aatacagaca ggattggcca gaactggtag 300
atggctggct gttgattatg aaaatgtcag acctgatata gtcctccttg gaaaggccct 360
ttctgggggc ttataccc 378

<210> 278
<211> 366
<212> DNA
<213> Homo sapiens

<400> 278

ggagggcaca ttccttttca cctcagagtc ggtcggggaa ggccacccag ataagatttg 60
tgaccaaacc agtgatgctg tccttgatgc ccaccttcag caggatcctg atgccaaagt 120
agcttgtgaa actgttgcta aaactggaat gatccttctt gctggggaaa ttacatccag 180
agctgctgtt gactaccaga aagtggttcg tgaagctgtt aaacacattg gatatgatga 240
ttcttccaaa ggttttgact acaagacttg taacgtgctg gtagccttgg agcaacagtc 300
accagatatt gctcaaggtg ttcatcttga cagaaatgaa gaagacattg gtgctggaga 360
ccaggg 366

<210> 279
<211> 435
<212> DNA
<213> Homo sapiens

<400> 279
cctaagaact gagacttgtg acacaaggcc aacgacctaa gattagccca gggttgtagc 60
tggaagacct acaacccaag gatggaaggc ccctgtcaca aagcctacct agatggatag 120
aggacccaag cgaaaaagat atctcaagac taacggccgg aatctggagg cccatgaccc 180
agaacccagg aaggatagaa gcttgaagac ctggggaaat cccaagatga gaaccctaaa 240
ccctacctct tttctattgt ttacacttct tactcttaga tatttccagt tctcctgttt 300
atctttaagc ctgattcttt tgagatgtac tttttgatgt tgccggttac ctttagattg 360
acaagtatta tgcctggcca gtcttgagcc agctttaaat cacagctttt acctatttgt 420
taggctatag tgttt 435

<210> 280
<211> 435
<212> DNA
<213> Homo sapiens

<400> 280
tctggatgag ctgctaactg agcacaggat gacctgggac ccagcccagc caccccgaga 60
cctgactgag gccttcctgg caaagaagga gaaggccaag gggagccctg agagcagctt 120
caatgatgag aacctgcgca tagtggtggg taacctgttc cttgccggga tggtgaccac 180
ctcgaccacg ctggcctggg gcctcctgct catgatccta cacctggatg tgcagcgtga 240
gcccagacct gtccgggcgg ccgctcgaaa ttccagcaca ctggcggccg ttactagtgg 300
atccgagctc ggtaccaagc ttggcgtaat catggtcata gctgtttcct gtgtgaaatt 360
gttatccgct cacaattcca cacaacatac gagccggaag cataaagtgt aaagcctggg 420
gtgcctaatg agtga 435

<210> 281
<211> 440
<212> DNA
<213> Homo sapiens

<400> 281
catctgatct ataaatgcgg tggcatcgac aaaagaacca ttgaaaaatt tgagaaggag 60
gctgctgaga tgggaaaggg ctccttcaag tatgcctggg tcttggataa actgaaagct 120
gagcgtgaac gtggtatcac cattgatatc tccttgtgga aatttgagac cagcaagtac 180
tatgtgacta tcattgatgc cccaggacac agagacttta tcaaaaacat gattacaggg 240
acatctcagg ctgactgtgc tgtcctgatt gttgctgctg gtgttggtga atttgaagct 300
ggtatctcca agaatgggca gacccgagag catgcccttc tggcttacac actgggtgtg 360
aaacaactaa ttgtcggtgt taacaaaatg gattccactg agcccccтac agccagaaga 420
gatatgagga aattgttaag 440

<210> 282
<211> 502
<212> DNA
<213> Homo sapiens

<400> 282
tctgtggcgc aggagccccc tcccccggca gctctgacgt ctccaccgca gggactggtg 60
cttctcggag ctcccactcc tcagactccg gtggaagtga cgtggacctg gatcccactg 120
atggcaagct cttccccagc gatggttttc gtgactgcaa gaaggggat cccaagcacg 180

ggaagcggaa acgaggccgg ccccgaaagc tgagcaaaga gtactgggac tgtctcgagg 240
gcaagaagag caagcacgcg cccagaggca cccacctgtg ggagttcatc cgggacatcc 300
tcatccaccc ggagctcaac gagggcctca tgaagtggga gaatcggcat gaaggcgtct 360
tcaagttcct gcgctccgag gctgtggccc aactatgggg ccaaaagaaa aagaacagca 420
acatgaccta cgagaagctg agccgggcca tgaggtacta ctacaaacgg gagatcctgg 480
aacgggtgga tggccggcga ct 502

<210> 283
<211> 433
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(433)
<223> n=A,T,C or G

<400> 283
ccatattaga ttactggaac atctaagcat cagtgtgtga ccatgcgaac aaaagacttc 60
ggggagtgtc tatttttaaa aaggtttatg tgtgtcgagg cagttgtaaa agatttactg 120
cagaatcaan cccactttta ggcttangac caggttctaa ctatctaaaa atattgactg 180
ataacaaaaa gtgttctaaa tgtggctatt ctgatccata nttgnttttt aaagaaaaaa 240
antgtntata cagaaagagt ntaaaagttc tgtgaattna atgcaaatta gncnccantc 300
ttgacttccc aaanacttga ttnatacctt tnactcctnt cnnttcctgn ncttcnttaa 360
nntcaatnat tnggnagtnn anggccntcn gnanaacacc nttncncgnt ccncgcaatc 420
canccgcctt nan 433

<210> 284
<211> 479
<212> DNA
<213> Homo sapiens

<400> 284
tctggaagga tcagggatct gagcaaagcc aagtttactt aagctaagcc acttgttcct 60
gggtcaagca gtttgttttc taataagcat cattcctgat cattagagca aagggatgaa 120
tgctcctctt ggaatgatac aggggatctg ccactgggag agtgttgctc agtgttagag 180
tagcagcaat gacagaatga cagcgactct ctgagtcaac ccagtacttt tagtaccccg 240
tcactatgtg aataaaggca gctagaaaat ggactcaatt ctgcaagcct tcatggcaac 300
agcccatatt aagacttcta gaacaagtta aaaaaaaatc ttccatttcc atccatgcat 360
gggaaaaggg ctttagtata gtttaggatg gatgtgtgta taataataaa atgataagat 420
atgcatagtg ggggaataaa gcctcagagt ccttccagta tggggaatcc attgtatct 479

<210> 285
<211> 435
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(435)
<223> n=A,T,C or G

<400> 285
ttttttttttt ttttttttttt tcaatanaaa tgccataatt tattccattg tataaaaaag 60
tcatccttat gtaacaaaat gtnttcttan aanaanaaat atattatttc aggtcataaa 120
taatcagcaa acatacaact gttggcaact aaaaaaaaac ccaacactgg tattttccat 180
cagngctgaa aacaaacctg cttaaanata tatttacagg gatagtncag tnctcaaaaa 240
caaaaattga ggtattttgg ttcttctagg agtagacaat gacattttgg gangggcaga 300
cccctnnccc aaaaaataaa ataagggnat nttcttcant atngaanann gggggcgccc 360
cggggaaaan naaaccttgg gnnggggggtt tggcccaagc ccttgaaaaa aaantttntt 420
tcccaaaaaa aacng 435

<210> 286
<211> 301
<212> DNA
<213> Homo sapiens

<400> 286
cctggtttct ggtggcctct atgaatccca tgtagggtgc agaccgtact ccatccctcc 60
ctgtgagcac cacgtcaacg gctcccggcc cccatgcacg ggggagggag atacccccaa 120
gtgtagcaag atctgtgagc ctggctacag cccgacctac aaacaggaca agcactacgg 180
atacaattcc tacagcgtct ccaatagcga gaaggacatc atggccgaga tctacaaaaa 240
cggccccgtg gagggagctt tctctgtgta ttcggacttc ctgctctaca agtcaggagt 300
g 301

<210> 287
<211> 432
<212> DNA
<213> Homo sapiens

<400> 287
tccagcttgt tgccagcatg agaaccgcca ttgatgacat tgaacgccgg gactggcagg 60
atgacttcag agttgccagc caagtcagcg atgtggcggt acagggggac ccccttctca 120
acggcaccag ctttgcagac ggcaagggac acccccagaa tggcgttcgc accaaactta 180
gatttatttt ctgttccatc catctcgatc atcagtttgt caatcttctc ttgttctgtg 240
acgttcagtt tcttgctaac cagggcaggc gcaatagttt tattgatgtg ctcaacagcc 300
tttgagacac ccttccccat atagcgagtc ttatcattgt cccggagctc tagggcctca 360
tagataccag ttgaagcacc actgggcaca gcagctctga agagaccttt tgaggtgaag 420
agatcaacct ca 432

<210> 288
<211> 326
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (254)
<223> n=A,T,C or G

<400> 288
tctggctcaa gtcaaagtcc tggtcctctt ctccgcctcc ttcttcatca tagtaataaa 60
cgttgtcccg ggtgtcatcc tctgggggca gtaagggctc tttgaccacc gctctcctcc 120
gaagaaacag caagagcagc agaatcagaa ttagcaaagc aagaattcct ccaagaatcc 180
ccagaatggc aggaatttgc aatcctgctt cgacaggctg tgccttccta cagacgccgg 240
cggccccttc acantcacac acgctgacct ctaaggtggt cacttggtct ttattctggt 300
tatccatgag cttgagattg attttg 326

<210> 289
<211> 451
<212> DNA
<213> Homo sapiens

<400> 289
gtcccggtgt ggctgtgccg ttggtcctgt gcggtcactt agccaagatg cctgaggaaa 60
cccagaccca agaccaaccg atggaggagg aggaggttga gacgttcgcc tttcaggcag 120
aaattgccca gttgatgtca ttgatcatca atactttcta ctcgaacaaa gagatctttc 180
tgagagagct catttcaaat tcatcagatg cattggacaa aatccggtat gaaagcttga 240
cagatcccag taaattagac tctgggaaag agctgcatat taaccttata ccgaacaaac 300
aagatcgaac tctcactatt gtggatactg gaattggaat gaccaaggct gacttgatca 360
ataaccttgg tactatcgcc aagtctggga ccaaagcgtt catggaagct ttgcaggctg 420
gtgcagatat ctctatgatt ggacctcggc c 451

<210> 290

<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (421)
<223> n=A,T,C or G

<400> 290
ttttttttt tcaaaacagt atattttatt ttacaatagc aaccaactcc ccagtttgtt 60
tcaattgtga catctagatg gcttaagatt actttctggt ggtcacccat gctgaacaat 120
atttttcaat cttccaaaca gcaaagactc aaaagagatt ctgcatttca catcagttca 180
caagttcaag agtcttccat ttatcttagc ttttggaata aattatcttt gaggtagaag 240
gacaatgacg aagccactta attccttgtg tctgcataaa agcagattta ttcatcacaa 300
cttcatttat gtgaataaag cagatgatga taaaatgttc tcttattctt gtttaatcag 360
tagtggtagt gatgccagaa acttgtaaat gcacttcaaa ccaattgtgg ctcaagtgta 420
ngtggttccc caaggctggt accaatgaga ctggggtttg ggaattagtt ggtcatcatc 480
cctcctgctg ccca 494

<210> 291
<211> 535
<212> DNA
<213> Homo sapiens

<400> 291
tcgcgtgctt aacatgaaaa caaactttgt gctgtttggt tcattgtatg cattgatgga 60
gtcttgtctc tcatcatggg gtgtctgacc atccaacctg cagtactcat aatttctcca 120
catgcaataa tcttccaaaa tgtccaatac ccttgtcatt tgactgaaga ttagtactcg 180
tgaaccttgt tcttttaact tagggagcag cttgtctaaa accaccattt tgccactgtt 240
ggttactaga tgcatatctg ttgtataagg tggaccaggt tctgctccat caaagagata 300
tggatgatta caacattttc tcaactgcat taggatgttc aataacctca ttttgtccat 360
cttgcctgct gagttgagta tatctatatc cttcattaat atccgagtat accattccct 420
ttgcattttg ctgaggccca catagatttt tacttccttc tttggaggca aactcttttc 480
aacatcagcc ttaattcgac gaaggaggaa tggacgcaaa accatatgaa gcctc 535

<210> 292
<211> 376
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(376)
<223> n=A,T,C or G

<400> 292
tacnagcccg tgctgatcga gatcctggtg gaggtgatgg atccttcctt cgtgtgcttg 60
aaaattggag cctgcccctc ggcccataag cccttgttgg gaactgagaa gtgtatatgg 120
ggcccaagct actggtgcca gaacacagag acagcagccc agtgcaatgc tgtcgagcat 180
tgcaaacgcc atgtgtggaa ctaggaggag gaatattcca tcttggcaga aaccacagca 240
ttggtttttt tctacttgtg tgtctggggg aatgaacgca cagatctgtt tgactttgtt 300
ataaaaatag ggctccccca cctcccccat ttttgtgtcc tttattgnag cattgctgtc 360
tgcaagggag ccccta 376

<210> 293
<211> 320
<212> DNA
<213> Homo sapiens

<400> 293
tcggctgctt cctggtctgg cggggatggg tttgctttgg aaatcctcta ggaggctcct 60

cctcgcatgg cctgcagtct ggcagcagcc ccgagttgtt tcctcgctga tcgatttctt 120
tcctccaggt agagttttct ttgcttatgt tgaattccat tgcctctttt ctcatcacag 180
aagtgatgtt ggaatcgttt cttttgtttg tctgatttat ggtttttta agtataaaca 240
aaagtttttt attagcattc tgaaagaagg aaagtaaaat gtacaagttt aataaaaagg 300
ggccttcccc tttagaatag 320

<210> 294
<211> 359
<212> DNA
<213> Homo sapiens

<400> 294
ctgtcataaa ctggtctgga gtttctgacg actccttgtt caccaaatgc accatttcct 60
gagacttgct ggcctctccg ttgagtccac ttggctttct gtcctccaca gctccattgc 120
cactgttgat cactagcttt ttcttctgcc cacaccttct tcgactgttg actgcaatgc 180
aaactgcaag aatcaaagcc aaggccaaga gggatgccaa gatgatcagc cattctggaa 240
tttggggtgt ccttatagga ccagaggttg tgtttgctcc accttcttga ctcccatgtg 300
agtgtccatc tgattcagat ccatgagtgg tatgggaccc cccactgggg tggaatgtg 359

<210> 295
<211> 584
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (558)
<223> n=A,T,C or G

<400> 295
cctgagttgg gctgactgcc agagacagac ccctctgggt ctcggtgaac cagccaggca 60
tttacctcag tggttggcac ctggaacctg tccagggccc tcacctgact gaggagccgc 120
cgggcagtga agtaattgtc caggtctatg ctcttggggt ggataccata gccatccaag 180
gtattcctca ggttgtggaa ctgggtctga gtataggcag aactgggccc caggatgatc 240
tcccggagtg ggggaagctg tgaggtcagg taagtatcca cgtccacccg taccccaatc 300
aaactcagca gaatggtgaa ctggagaagt ccttccgtta agtatttctt cagagaaagc 360
attgctgaag gaccagaatg tttatgcttt ttggttttta aaatcttcca aaagacaaat 420
caaggccact gctctgccgc tccagccagc aggttaccct cctcagtgtc aaaccccgta 480
ccccaccctg gcagaacaca agggatgagc tccctgacgg ccccagagga aagcacaccc 540
tgtggagcca aggccaanga cacactccag accacattca cttt 584

<210> 296
<211> 287
<212> DNA
<213> Homo sapiens

<400> 296
ccttatcatt cattcttagc tcttaattgt tcattttgag ctgaaatgct gcattttaat 60
tttaaccaaa acatgtctcc tatcctggtt tttgtagcct tcctccacat cctttctaaa 120
caagatttta aagacatgta ggtgtttgtt catctgtaac tctaaaagat cctttttaaa 180
ttcagtccta agaaagagga gtgcttgtcc cctaagagtg tttaatggca aggcagccct 240
gtctgaagga cacttcctgc ctaagggaga gtggtatttg cagacta 287

<210> 297
<211> 457
<212> DNA
<213> Homo sapiens

<400> 297
ccaattgaaa caaacagttc tgagaccgtt cttccaccac tgattaagag tggggtggca 60
ggtattaggg ataatattca tttagccttc tgagctttct gggcagactt ggtgaccttg 120
ccagctccag cagccttctt gtccactgct ttgatgacac ccaccgcaac tgtctgtctc 180

atatcacgaa cagcaaagcg acccaaaggt ggatagtctg agaagctctc aacacacatg 240
ggcttgccag gaaccatatc aacaatggca gcatcaccag acttcaagaa tttagggcca 300
tcttccagct ttttaccaga acggcgatca atcttttcct tcagctcagc aaacttgcat 360
gcaatgtgag ccgtgtggca atccaataca ggggcatagc cggcgcttat ttggcctgga 420
tggttcagga taatcacctg agcagtgaag ccagacc 457

<210> 298
<211> 469
<212> DNA
<213> Homo sapiens

<400> 298
tctttgactt tccttgtcta cctcctctgg agatctcaaa ttctccaggt tccatgctcc 60
cagagatctc aatgattcct gattctcctc ttccaggagt ctgaatgtct cttggttcac 120
ttccacagac tccagtggtt cttgaatttc cttttctaga ggattcattg ccccctgatt 180
tatttcttct ggagtccaca gtggtgcttg agtttctgga gatttcagtg tttccaggtt 240
ctcttgtccc gcagacttca gtgattctag gatctctgtt tctaaagatt ttactgcctc 300
tatgctctct tctttgagtg actttaagaa ctcttgattc tcattttcaa gaggtctagc 360
tatctcctgg tcaagagact tcagtggttc tagatccact ttttctgggg gtcttaatgt 420
catctgatcc tgttccccta gagacctccg tcgctgttga gtctctttt 469

<210> 299
<211> 165
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(165)
<223> n=A,T,C or G

<400> 299
tctgtggaga ggatgaggtt gagggaggtg gggtatntcg ctgctctgac cttaggtaga 60
gtcctccaca gaagcatcaa antggactgg cacatatgga ctcccttcac aggccacaat 120
gatgtgtctc tccttcgggc tggnccggta tgcacagttg gggta 165

<210> 300
<211> 506
<212> DNA
<213> Homo sapiens

<400> 300
tctgaggaaa gtttgggctt attagtattt gctccagcga acctccaagt tttctccatt 60
gcggacaacg taactaccag ctccttggct cagtggttcg cctccactca gaagttccca 120
gtaggttctg tcattattgt tggcacatag gccctgaata caggtgatat agggccccca 180
tgagcgctcc tccattgtga aaccaaatat agtatcattc attttctggg ctttctccat 240
cacactgagg aagacagaac catttagcac agtgacattg gtgaaatatg tttcattgat 300
tctcacagag taattgacgg agatatatga ttgtgagtca ggaggtgtca cagttatagg 360
ctcatcagcg gagatgttga agttacctga agcagagacg caagaagagt ctttgttaat 420
atccaagaag gtctttccca tcagggcagg taagacctgg gctgcagcgt ttggattgct 480
gaatgctcct tgagaaattt ccgtga 506

<210> 301
<211> 304
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(304)
<223> n=A,T,C or G

<400> 301
tcctaaggca gagcccccat cacctcaggc ttctcagttc ccttagccgt cttactcaac 60
tgccccttc ctctccctca gaatttgtgt ttgctgcctc tatcttgttt tttgtttttt 120
cttctggggg gggtctagaa cagtgcctgg cacatagtag gcgctcaata aatacttgtt 180
tgttgaatgt ctcctctctc tttccactct gggaaaccta ngnttctgcc attctgggtg 240
accctgtatt tntttctggt gcccattcca tttgnccagn taatacttcc tcttaaaaat 300
ctcc 304

<210> 302
<211> 492
<212> DNA
<213> Homo sapiens

<400> 302
ttttcagtaa gcaacttttc catgctctta atgtattcct ttttagtagg aatccggaag 60
tattagattg aatggaaaag cacttgccat ctctgtctag gggtcacaaa ttgaaatggc 120
tcctgtatca catacggagg tcttgtgtat ctgtggcaac agggagtttc cttattcact 180
ctttatttgc tgctgtttaa gttgccaacc tcccctccca ataaaaattc acttacacct 240
cctgcctttg tagttctggt attcacttta ctatgtgata gaagtagcat gttgctgcca 300
gaatacaagc attgcttttg gcaaattaaa gtgcatgtca tttcttaata cactagaaag 360
gggaaataaa ttaaagtaca caagtccaag tctaaaactt tagtactttt ccatgcagat 420
ttgtgcacat gtgagagggt gtccagtttg tctagtgatt gttatttaga gagttggacc 480
actattgtgt gt 492

<210> 303
<211> 470
<212> DNA
<213> Homo sapiens

<400> 303
tctggggcag caggtactcc ctacggcact agtctacagg gggaaggacg ctctgtgctg 60
gcagcggtgg ctcacatggc ctgtctgcac tgtaaccaca ggctgggatg tagccaggac 120
ttggtctcct tggaagacag gtctgatgtt tggccaatcc agtccttcag accctgcctg 180
aaacttgtat cttacgtgaa cttaaagaat aaaatgcatt tctaccccga tctcgccccc 240
aggactggca cgacaggccc acggcagatt agatctttc ccagtactga tcggtgcgtg 300
gaattccagc caccacttct gattcgattc cacagtgatc ctgtcctctg agtattttaa 360
agaagccatt gtcaccccag tcagtgttcc aggagttggc aaccagccag tagggtgtgc 420
cattctccac tccccagccc aggatgcgga tggcatggac ctcggccgcg 470

<210> 304
<211> 79
<212> DNA
<213> Homo sapiens

<400> 304
tgtcccattg ttaactcagc ctcaaatctc aactgtcagg ccctacaaag aaaatggaga 60
gcctcttctg gtggatgcg 79

<210> 305
<211> 476
<212> DNA
<213> Homo sapiens

<400> 305
tcactgagcc accctacagc cagaagagat atgaggaaat tgttaaggaa gtcagcactt 60
acattaagaa aattggctac aaccccgaca cagtagcatt tgtgccaatt tctggttgga 120
atggtgacaa catgctggag ccaagtgcta acgtaagtgg ctttcaagac cattgttaaa 180
aagctctggg aatggcgatt tcatgcttac acaaattggc atgcttgtgt ttcagatgcc 240
ttggttcaag ggatggaaag tcacccgtaa ggatggcaat gccagtggaa ccacgctgct 300
tgaggctctg gactgcatcc taccaccaac tcgtccaact gacaagccct tgcgcctgcc 360
tctccaggat gtctacaaaa ttggtggtaa gttggctgta aacaaagttg aatttgagtt 420
gatagagtac tgtctgcctt cataggtatt tagtatgctg taaatatttt taggta 476

<210> 306
<211> 404
<212> DNA
<213> Homo sapiens

<400> 306
tctgtctcgg agctcagggc gcagccagca cacacaggag cccacaggac agccacgtct 60
tcacagaaac tacagaagtc aggacccagg cgaggacctc aggaacaagt gccccctgca 120
gacagagaga cgcagtagca acagcttctg aacaactaca taataatgcg gggagaatcc 180
tgaagaccac tgcatcccac aagcactgac aaccacttca ggattttatt tcctccactc 240
taacccccag atccatttat gagaagtgag tgaggatggc aggggcatgg agggtgaagg 300
gacagcaagg atggtctgag ggcctggaaa caatagaaaa tcttcgtcct ttagcatatc 360
ctggactaga aaacaagagt tggagaagag gggggttgat acta 404

<210> 307
<211> 260
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(260)
<223> n=A,T,C or G

<400> 307
tcctgcctan acatctgtga gggcctcaag ggctgctgcc tcgactttct ccctagctaa 60
gtccacccgt ccagggacac agccagggca ctgctctgtg ctgacttcca ctgcagccaa 120
gggtcaaaat gaagcatctg cggaggccag gactccttgg catcggacac agtcagggga 180
aaagccaccc tgactctgca ggacagaggg tctagggtca tttggcagga gaacactggt 240
gtgccaaggg aagcnancat 260

<210> 308
<211> 449
<212> DNA
<213> Homo sapiens

<400> 308
tctgtgctcc cgactcctcc atctcaggta ccaccgactg cactgggcgg ggccctctgg 60
ggggaaaggc tccacggggc agggatacat ctcgaggcca gtcatcctct ggaggcagcc 120
caatcaggtc aaagattttg cccaactggt cggcttcaga gtttccacag aagagaggct 180
ttcgacgaaa catctctgca aagatacagc caacactcca catgtccaca ggtgttgcat 240
atgtggactg cagaagaact tcgggagctc ggtaccagag tgtaacaacc ttgatcgttt 300
cggctggcaa gcctggtggg ggtgccttgt ccagatatgt ccttaggtcc tggtctacat 360
gctcaaacac cagggttacc ttgatctccc ggtcagttcg ggatgtggca cagacgtcca 420
tcagccggac aacattggga tgctcaaaa 449

<210> 309
<211> 411
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (384)
<223> n=A,T,C or G

<400> 309
ctgtggaaac ctggggtgcc gggtaaatgg agaactccag cttggatttc ttgccataat 60
caactgagag acgttccatg agcagggagg tgaacccaga accagttccc ccaccaaagc 120
tgtggaaaac caagaagccc tgaagaccgg tgcactggtc agccagcttg cgaattcggt 180
ccaacacaag gtcaatgatc tccttgccaa tggtgtagtg ccctcgggca tagttattgg 240

cagcatcttc cttgcctgtg atgagctgct cagggtggaa gagctggcgg taggtgccag 300
tgcgaacttc atcaatgact gtgggttcca agtctacaaa cacagcccgg ggcacgtgct 360
tgccagcgcc cgtctcactt gaanaagggt gtttgaagga agtcatctcc t 411

<210> 310
<211> 320
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (250)
<223> n=A,T,C or G

<400> 310
tcctcgtcca gcttgactcg attagtcctc ataaggtaag caaggcagat ggtggctgac 60
cgggaaatgc ctgcctggca gtggacaaac acccttcctc cagcattctt gatggagtct 120
atgaagtcaa tggcctcgtt gaaccaggag ctgatgtctg ccttgtggtt gtcctccaca 180
gggatgctct tgtactggta gtgaccctca aaatggttgg gacaattggc tgagacgttg 240
atcaaggcan ttatgcccaa ggcatccagc atgtccttgc gggaagcgtg atacgcactg 300
cccaggtaca gaaagggcag 320

<210> 311
<211> 539
<212> DNA
<213> Homo sapiens

<400> 311
tctggcccat gaagctgaag ttgggagaga tgatgcttcg cctctgcttc acaaactcaa 60
aggcctcgtc cagcttgact cgattagtcc tcataaggta agcaaggcag atggtggctg 120
accgggaaat gcctgcctgg cagtggacaa acacccttcc tccagcattc ttgatggagt 180
ctatgaagtc aatggcctcg ttgaaccagg agctgatgtc tgccttgtgg ttgtcctcca 240
cagggatgct cttgtactgg tagtgaccct caaaatggtt gggacaattg gctgagacgt 300
tgatcaaggc agttatgccc aaggcatcca gcatgtcctt gcgggaagcg tgatacgcac 360
tgcccaggta cagaaagggc aggatttcca ccgggccacc ctgaaatcca gaaatatcca 420
acattcatca agcttgctca aagccaaggc cagtgcccat acccacaaaa actttctgct 480
ggaaaagtca atttcagata ccgagtgaac tcagttctgt tgctggagga taaataaat 539

<210> 312
<211> 475
<212> DNA
<213> Homo sapiens

<400> 312
tcaaggatct tcctaaagcc accatgtgag aggattcgga cgagagtctg agctgtatgg 60
cagaccatgt cctgctgttc tagggtcatg actgtgtgta ctctaaagtt gccactctca 120
caggggtcag tgatacccac tgaacctggc aggaacagtc ctgcagccag aatctgcaag 180
cagcgcctgt atgcaacgtt tagggccaaa ggctgtctgg tggggttgtt catcacagca 240
taatggccta gtaggtcaag gatccagggt gtgaggggct caaagccagg aaaacgaatc 300
ctcaagtcct tcagtagtct gatgagaact ttaactgtgg actgagaagc attttcctcg 360
aaccagcggg catgtcggat ggctgctaag gcactctgca atactttgat atccaaatgg 420
agttctggat ccagttttcg aagattgggt ggcactgttg taatgagaat cttca 475

<210> 313
<211> 456
<212> DNA
<213> Homo sapiens

<400> 313
tccacttaaa gggtgcctct gccaactggt ggaatcatcg ccacttccag caccacgcca 60
agcctaacat cttccacaag gatcccgatg tgaacatgct gcacgtgttt gttctgggcg 120
aatggcagcc catcgagtac ggcaagaaga agctgaaata cctgccctac aatcaccagc 180

acgaatactt cttcctgatt gggccgccgc tgctcatccc catgtatttc cagtaccaga 240
tcatcatgac catgatcgtc cataagaact gggtggacct ggcctgggcc gtcagctact 300
acatccggtt cttcatcacc tacatccctt tctacggcat cctgggagcc ctcctttcc 360
tcaacttcat caggttcctg gagagccact ggtttgtgtg ggtcacacag atgaatcaca 420
tcgtcatgga gattgaccag gaggacctcg gcccgc 456

<210> 314
<211> 477
<212> DNA
<213> Homo sapiens

<400> 314
tgcgtgggct tctggaagcc tggatctgga atcattcacc agattattct ggaaaactat 60
gcgtaccctg gtgttcttct gattggcact gactcccaca cccccaatgg tggcggcctt 120
gggggcatct gcattggagt tgggggtgcc gatgctgtgg atgtcatggc tgggatcccc 180
tgggagctga agtgccccaa ggtgattggc gtgaagctga cgggctctct ctccggttgg 240
tcctcaccca aagatgtgat cctgaaggtg gcaggcatcc tcacggtgaa aggtggcaca 300
ggtgcaatcg tggaatacca cgggcctggt gtagactcca tctcctgcac tggcatggcg 360
acaatctgca acatgggtgc agaaattggg gccaccactt ccgtgttccc ttacaaccac 420
aggatgaaga agtatctgag caagaccggc cgggaagaca ttgccaatct agctgat 477

<210> 315
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 315
caggtactgg atgtcaggtc tgcgaaactt cttanatttt gacctcagtc cataaaccac 60
actatcacct cggccatcat atgtgtctac tgtggggaca actggagtga aaacttcggt 120
tgctgcaggt ccgtgggaaa atcagtgacc agttcatcag attcatcaga atggtgagac 180
tcatcagact ggtgagaatc atcagtgtca tctacatcat cagagtcgtt cgagtcaatg 240
g 241

<210> 316
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 316
nttntgtgat agtgtggttt atggactgag gncaaaatnt aagaagtttc gcagacctga 60
catccaancc tgcccgngcg gncgctcgaa aggncgaatt ctgcagatat ccatcacact 120
ggcggccgct cgagcatgca tctagagggc ccaattcgcc ctatantgag tnatattaca 180
attcactggc cgtcnnttta caacgtcgtg actgggaaaa ccctggcgtt acccaactta 240
a 241

<210> 317
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> (1)...(241)
<223> n = A,T,C or G

<400> 317
aggtaccctg ctcancagcc tgggngcctg ggttgtctcc ttgtccatcc actggtccat 60
tctgctctgc attttttgt tcctcttttg gaggttccac tttgggtttg ggctttgaaa 120
ttatagggct acaantacct cggccgaaac cacnctaagg gcgaattctg cagatatcca 180
tcacactggc ggncgctcga gcatgcatct agagggccca attcgcccta tagtgagtcg 240
t 241

<210> 318
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 318
cgngnacaan ntacattgat gganggtntg nggntctgan tntttantta cantggagca 60
ttaatatttt cttnaacgtn cctcaccttc ctgaantaaa nactctgggt tgtagcgctc 120
tgtgctnana accacntnaa ctttacatcc ctcttttgga ttaatccact gcgcggccac 180
ctctgccgcg accacgctaa gggcnaattc tgcagatatc catcacactg gcggccgctc 240
n 241

<210> 319
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 319
caggtactga tcggtgcgtg gaantccagc caccanttnt gattcgattc cacagtgatc 60
ctgtcctctg agtattttaa agaagccatt gtcaccccag tcagtgttcc aggagttggc 120
aaccagccag tagggtgtgc cattctccac tccccagccc aggatgcgga tggcatggcc 180
acccatcatc tctccggtga cgtgttggta cctcggccgc gaccacgcta agggcgaatt 240
c 241

<210> 320
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 320
ggcaggtacc aacagagctt agtaatntct aaaaagaaaa aatgatcttt ttccgacttc 60
taaacaagtg actatactag cataaatcat tctagtaaaa cagctaaggt atagacattc 120
taataatttg ggaaaaccta tgattacaag tgaaaactca gaaatgcaaa gatgttggtt 180
ttttgtttct cagtctgctt tagcttttaa ctctnnnaan cncatgcaca cttgnaactc 240
t 241

<210> 321

<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 321
angtaccaac agagcttagt aattnntaaa aagaaaaaat gatctttttc cgacttctaa 60
acaagtgact atactagcat aaatcattct agtaaaacag ctaaggtata gacattctaa 120
taatttggga aaacctatga ttacaagtga aaactcagaa atgcaaagat gttggttttt 180
tgtttctcag tctgctttag cttttaactc tggaagcgca tgcacacntg aactctgctc 240
a 241

<210> 322
<211> 241
<212> DNA
<213> Homo sapiens

<400> 322
ggtaccaaca gagcttagta atttctaaaa agaaaaaatg atctttttcc gacttctaaa 60
caagtgacta tactagcata aatcattctt ctagtaaaac agctaaggta tagacattct 120
aataatttgg gaaaacctat gattacaagt aaaaactcag aaatgcaaag atgttggttt 180
tttgtttctc agtctgcttt agcttttaac tctggaagcg catgcacact gaactctgct 240
c 241

<210> 323
<211> 241
<212> DNA
<213> Homo sapiens

<400> 323
cgaggtactg tcgtatcctc agccttgttc tatttcttta ttttagcttt acagagatta 60
ggtctcaagt tatgagaatc tccatggctt tcaggggcta aacttttctg ccattctttt 120
gctcttaccg ggctcagaag gacatgtcag gtgggatacg tgtttctctt tcagagctga 180
agaaagggtc tgagctgcgg aatcagtaga gaaagccttg gtctcagtga ctccttggct 240
t 241

<210> 324
<211> 241
<212> DNA
<213> Homo sapiens

<400> 324
aggtactgtc gtatcctcag ccttgttcta tttctttatt ttagctttac agagattagg 60
tctcaagtta tgagaatctc catggctttc aggggctaaa cttttctgcc attcttttgc 120
tcttaccggg ctcagaagga catgtcaggt gggatacgtg tttctctttc agagctgaag 180
aaagggtctg agctgcggaa tcagtagaga aagccttggt ctcagtgact ccttggcttt 240
c 241

<210> 325
<211> 241
<212> DNA
<213> Homo sapiens

<400> 325
ggcaggtaca tttgttttgc ccagccatca ctctttttttg tgaggagcct aaatacattc 60
ttcctggggt ccagagtccc cattcaaggc agtcaagtta agacactaac ttggcccttt 120
cctgatggaa atatttcctc catagcagaa gttgtgttct gacaagactg agagagttac 180
atgttgggaa aaaaaaagaa gcattaactt agtagaactg aaccaggagc attaagttct 240

g 241

<210> 326
<211> 241
<212> DNA
<213> Homo sapiens

<400> 326
gcaggtacat ttgttttgcc cagccatcac tctttttgt gaggagccta aatacattct 60
tcctggggtc cagagtcccc attcaaggca gtcaagttaa gacactaact tggccctttc 120
ctgatggaaa tatttcctcc atagcagaag ttgtgttctg acaagactga gagagttaca 180
tgttgggaaa aaaaagaagc attaacttag tagaactgat ccaggagcat taagttctga 240
a 241

<210> 327
<211> 241
<212> DNA
<213> Homo sapiens

<400> 327
ggtaccagac caagtgaatg cgacagggaa ttatttcctg tgttgataat tcatgaagta 60
gaacagtata atcaaaatca attgtatcat cattagtttt ccactgcctc acactagtga 120
gctgtgccaa gtagtagtgt gacacctgtg ttgtcatttc ccacatcacg taagagcttc 180
caaggaaagc caaatcccag atgagtctca gagagggatc aatatgtcca tgattatcag 240
g 241

<210> 328
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 328
ggtacnagac caaatgaang ccacagggaa ttatttcctg tgttgataat tcatgaagta 60
gaacantata atcaaaatca attgtatcat cattagtttt ccactgcctc acactagtga 120
gctgtgccaa gtagtagtgt gacacctgtg ttgtcatttc ccacatcacg taagagcttc 180
caaggaaagc caaatcccag atgagtctca gagagggatc aatatgtcca tnatcatcan 240
g 241

<210> 329
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 329
ttcaggtcga gttggctgca gatttgtggt gcnttctgag ccgtctgtcc tgcgccaaaa 60
ngcttcaaag tattattaaa aacatatgga tccccatgaa gccctactac accaaagttt 120
accaggagat ttggatagga atggggctga tgggcttcat cgtttataaa atccgggctg 180
ctgataagaa gtaaggcttt gaaagcttca gcgcctgctn ctggtcanna ctaaccatan 240
n 241

<210> 330
<211> 241

<212> DNA
<213> Homo sapiens

<400> 330
ttttgtgcag atttgtggtg cgttctgagc cgtctgtcct gcgccaagat gcttcaaagt 60
attattaaaa acatatggat ccccatgaag ccctactaca ccaaagttta ccaggagatt 120
tggataggaa tggggctgat gggcttcatc gtttataaaa tccgggctgc tgataaaaga 180
agtaaggctt tgaaagcttc agcgcctgct cctggtcatc actaaccaga tttacttgga 240
g 241

<210> 331
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 331
nttttaggna ctttgggctc cagacttcac tggtcttagg nattgaaacc atcacctggn 60
ntgcattcct catgactgag gttaacttaa aacaaaaatg gtaggaaagc tttcctatnc 120
ttcnggtaag anacaaatnt nctttaaaaa aangtggaag gcatgacnta cgtgagaact 180
gcacaaactg gccactgaca aaaatgaccc ccatttgtgt gacttcattg agacacatta 240
c 241

<210> 332
<211> 241
<212> DNA
<213> Homo sapiens

<400> 332
tgtgaggaga gggaacatgc tgagaaactg atgaagctgc agaaccaacg aggtggccga 60
atcttccttc aggatatcaa gaaaccagac tgtgatgact gggagagcgg gctgaatgca 120
atggagtgtg cattacattt ggaaaaaaat gtgaatcagt cactactgga actgcacaaa 180
ctggccactg acaaaaatga cccccatttg tgtgacttca ttgagacaca ttacctgaat 240
g 241

<210> 333
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 333
caggtacaag ctttttttt ttttttttt ttttttttt ttgnaaatac tnttattgn 60
aaatattcta tcctaaattc catatagcca attaattntt acanaatntt ttgttaattt 120
ttgngngtat aaattttaca aaaataaagg gtatgtttgt tgcacacaac ttacaaataa 180
taataaactn tttattgnaa atattnttta ttgnaaatat tctttatcct aaattccata 240
t 241

<210> 334
<211> 241
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 334
tacctgctgn aggggntgaa gncntctctg ctgccccagg catctgcanc ccctgctgct 60
ggttctgccc ctgctgcagc agaggagaag aaagatgaga agaaggagga gtctgaagag 120
tcagatgatg acatgggatt tggccttttt gattaaannc ctgctcccct gcaaataaag 180
ccttttaca caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aagcttgtac ctgcccnggc 240
g 241

<210> 335
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 335
ctatgtgctg ggatgactat ggagacccaa atgtctcana atgtatgtcc cagaaacctg 60
tggctgcttc aaccattgac agttttgctg ctgctggctt ctgcagacag tcaagctgca 120
gctcccccaa aggctgtgct gaaacttgag cccccgtgga tcaacgtgct ccaggaggac 180
tctgtgactc tgacatgcca gggggctcgc agccctgaga gcgactccat tcagtggttc 240
c 241

<210> 336
<211> 241
<212> DNA
<213> Homo sapiens

<400> 336
taccaaccta tgcagccaag caacctcagc agttcccatc aaggccacct ccaccacaac 60
cgaaagtatc atctcaggga aacttaattc ctgcccgtcc tgctcctgca cctcctttat 120
atagttccct cacttgattt ttttaacctt ctttttgcaa atgtcttcag ggaactgagc 180
taatactttt ttttttcttg atgttttctt gaaaagcctt tctgttgcaa ctatgaatga 240
a 241

<210> 337
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 337
ggtactgtat gtagctgcac tacaacagat tcttaccgtc tccacanagg tcatanattg 60
taaatggtna atactgactt ttttttttatt cccttgactc aagacagcta acttcatttt 120
cagaactgtt ttaaaccttt gtgtgctggt ttataaaata atgtgtgtaa tccttgttgc 180
tttcctgata ccagactgtt tcccgtggtt ggttagaata tattttgntt tgatgcttat 240
a 241

<210> 338
<211> 241
<212> DNA
<213> Homo sapiens

<400> 338
aggtacaggt gtgcgctgag ccgagtttac acggaaagga taaagcccat ttagtttctt 60
ctcaaatgga gttttccact ttcctttgaa gtagacagca ttcaccagga tcatcctggt 120
atccccatct acagaacctt caggtaacaa gtttgggatt ttgcctttgg tttgagtctt 180
gacccaggaa ttaatctttt ttctagcttc ttctgcacat tctaggaagt ctactgcctg 240
g 241

<210> 339
<211> 241
<212> DNA
<213> Homo sapiens

<400> 339
taccgacggc tcctggaggg agagagtgaa gggacacggg aagaatcaaa gtcgagcatg 60
aaagtgtctg caactccaaa gatcaaggcc ataacccagg agaccatcaa cggaagatta 120
gttctttgtc aagtgaatga aatccaaaag cacgcatgag accaatgaaa gtttccgcct 180
gttgtaaaat ctattttccc ccaaggaaag tccttgcaca gacaccagtg agtgagttct 240
a 241

<210> 340
<211> 241
<212> DNA
<213> Homo sapiens

<400> 340
gtagccctca cacacacatg cccgtaacag gatttatcac aagacacgcc tgcatgtaga 60
ccagacacag ggcgtatgga aagcacgtcc tcaagactgt agtattccag atgagctgca 120
gatgcttacc taccacggcc gtctccacca gaaaaccatc gccaactcct gcgatcagct 180
tgtgacttac aaaccttgtt taaaagctgc ttacatggac ttctgtcctt taaaagcttc 240
c 241

<210> 341
<211> 241
<212> DNA
<213> Homo sapiens

<400> 341
gtaccgccta ctttcgtctc atgtctccga acttcttgct gatggccgtt ccaacgttgc 60
tgaaagctgc agttgccttt tgccctgcgt gactcagggt ttcatgtgtt ttcttgtagg 120
cagtggtagt ctgcatgtca tgccagcttt tgctgaagtt ctgttttaat tcattcatca 180
ggttcatgcc gagttttgtt ttatctcaac tagatgcctt tctttcgctg acaaaacttg 240
t 241

<210> 342
<211> 241
<212> DNA
<213> Homo sapiens

<400> 342
gtacattggt gctataaata taaatgctac ttatgaagca tgaaattaag cttctttttt 60
cttcaagttt tttctcttgt ctagcaatct gttaggcttc tgaaccaaga ccaaatgttt 120
acgttcctct gctgcatacc aacgttactc caaacaataa aaatctatca tttctgctct 180
gtgctgagga atggaaaatg aaacccccac cccctgaccc ctaggactat acagtggaaa 240
c 241

<210> 343
<211> 241
<212> DNA
<213> Homo sapiens

<400> 343
gtacatgtgg tagcagtaat ttttttgaag caactgcact gacattcatt tgagttttct 60

ctcattatca gattctgttc caaacaagta ttctgtagat ccaaatggat taccagtgtg 120
ctacagactt cttattatag aacagcattc tattctacat caaaaatagt ttgtgtaagt 180
tagttttggt taccatctaa aatattttta aatgttcttt acataaaaat ttatgttgtg 240
t 241

<210> 344
<211> 241
<212> DNA
<213> Homo sapiens

<400> 344
ggtacaaaat tgttggaatt tagctaatag aaaaacatag taaatattta caaaaacgtt 60
gataacatta ctcaagtcac acacatataa caatgtagac aggtcttaac aaagtttaca 120
aattgaaatt atggagattt cccaaaatga atctaatagc tcattgctga gcatggttat 180
caatataaca tttaagatct tggatcaaat gttgtccccg agtcttctgc aatccagtcc 240
t 241

<210> 345
<211> 241
<212> DNA
<213> Homo sapiens

<400> 345
ggtacgaagc tgagcgcacg ggggttgccc cagcgtggag cctggacctc aaacttcacg 60
gaaaatgctc tctctctttg acaggcttcc agctgtctcc taatttcctg gatgaactct 120
ccccggcgat ttaactgatc ctgaaaagtg gtgagaggac tgaggaagac aaccaggtca 180
gcgttagatc ggcctctgag ggtggtgccc ttgcctgagg agccaccctt taccaccttg 240
g 241

<210> 346
<211> 241
<212> DNA
<213> Homo sapiens

<400> 346
caggtaccac tgagcctgag atggggatga gggcagagag aggggagccc cctcttccac 60
tcagttgttc ctactcagac tgttgcactc taaacctagg gaggttgaag aatgagaccc 120
ttaggtttta acacgaatcc tgacaccacc atctataggg tcccaacttg gttattgtag 180
gcaaccttcc ctctctcctt ggtgaagaac atcccaagcc agaaagaagt taactacagt 240
g 241

<210> 347
<211> 241
<212> DNA
<213> Homo sapiens

<400> 347
aggtacatct aaaggcatga agcactcaat tgggcaatta acattagtgt ttgttctctg 60
atggtatctc tgagaatact ggttgtagga ctggccagta gtgccttcgg gactgggttc 120
acccccaggt ctgcggcagt tgtcacagcg ccagccccgc tggcctccaa agcatgtgca 180
ggagcaaatg gcaccgagat attccttctg ccactgttct cctacgtggt atgtcttccc 240
a 241

<210> 348
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 348
angtacttgg caagattnga tgctcttgng ctcantgaca tcattcataa cttgtnngtg 60
tgancagagg aggagnncat catcntgtcc tcattcgtca gnnncctctc ctctctgaat 120
ctcaaacaag ttgataatgg agaaaaattt gaattctcag gattgaggct ggactggttc 180
cgcctacang catacactag cgtggctaag gcccctctgc accctgcatg anaaccctga 240
c 241

<210> 349
<211> 241
<212> DNA
<213> Homo sapiens

<400> 349
gcaggtacca tttgtctgac ctctgtaaaa aatgtgatcc tacagaagtg gagctggata 60
atcagatagt tactgctacc cagagcaata tctgtgatga agacagtgct acagagacct 120
gctacactta tgacagaaac aagtgctaca cagctgtggt cccactcgta tatggtggtg 180
agaccaaaat ggtggaaaca gccttaaccc cagatgcctg ctatcctgac taatttaagt 240
c 241

<210> 350
<211> 241
<212> DNA
<213> Homo sapiens

<400> 350
aggtactgtg gatatttaaa atatcacagt aacaagatca tgcttgttcc tacagtattg 60
cgggccagac acttaagtga aagcagaagt gtttgggtga ctttcctact taaaattttg 120
gtcatatcat ttcaaaacat ttgcatcttg gttggctgca tatgctttcc tattgatccc 180
aaaccaaatc ttagaatcac ttcatttaaa atactgagcg gtattgaata cttcgaagca 240
g 241

<210> 351
<211> 241
<212> DNA
<213> Homo sapiens

<400> 351
tacagaaatc atttggagcc gttttgagac agaagtagag gctctgtcaa gtcaatactg 60
cattgcagct tggtccactg aagaagccac gcctgagata caaaagatgc actacacttg 120
acccgcttta tgttcgcttc ctctcccctt ctctctcatc aactttatta ggttaaaaca 180
ccacatacag gctttctcca aatgactccc tatgtctggg gtttggttag aattttatgc 240
c 241

<210> 352
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 352
gtaccctgtn gagctgcacc aagattannt ggggccatca tgactgcanc cacnacgang 60
acgcaggcgt gnagtgcatc gtctgacccg gaaacccttt cacttctctg ctcccgaggt 120
gtcctcnggc tcatatgtgg gaaggcanan gatctctgan gagttnctg gggacaactg 180
ancagcctct ggagaggggc cattaataaa gctcaacatc attggcaaaa aaaaaaaaaa 240
a 241

<210> 353

<211> 241
<212> DNA
<213> Homo sapiens

<400> 353
aggtaccagt gcattaattt gggcaaggaa agtgtcataa tttgatactg tatctgtttt 60
ccttcaaagt atagagcttt tggggaagga aagtattgaa ctgggggttg gtctggccta 120
ctgggctgac attaactaca attatgggaa atgcaaaagt tgtttggata tggtagtgtg 180
tggttctctt ttggaatttt tttcaggtga tttaataata atttaaaact actataaaaa 240
c 241

<210> 354
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 354
ngcaggtccg ggcaggtacc aagattcatt ctcatcaaaa actagaaaca gaagggcaaa 60
ttccagtttc cttctgggat tgaatacttt caagtaaggt cttcgacaaa caatcagggg 120
gccaattaat ccactgtaga ggtccttaac ttgatccaca gttgaataat aagcccatgg 180
aatacaagca gaatcctctg ttccagctcc agatctttct gggattttcc atacgtaagt 240
g 241

<210> 355
<211> 241
<212> DNA
<213> Homo sapiens

<400> 355
ggtacccacc ctaaatttga actcttatca agaggctgat gaatctgacc atcaaatagg 60
ataggatgga ccttttttg agttcattgt ataaacaaat tttctgattt ggacttaatt 120
cccaaaggat taggtctact cctgctcatt cactctttca aagctctgtc cactctaact 180
tttctccagt gtcatagata gggaattgct cactgcgtgc ctagtctttc ttcacttacc 240
t 241

<210> 356
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 356
aggtactgta attgagcatc cggaatntgg agaagtaatt tagctacagg gtgaccaacg 60
caagaacata tgccagttcc tcgtagagat tggactggct aaggacgatc agctgaaggt 120
tcatgggttt taagtgcttg tggctcactg aagcttaagt gaggatttcc ttgcaatgag 180
tagaatttcc cttctctccc ttgtcacagg tttaaaaacc tcacagcttg tataatgtaa 240
c 241

<210> 357
<211> 241
<212> DNA
<213> Homo sapiens

<400> 357
ttttgtacca ccgatatgat caaggaaaat tctgcccatt tttatggctg aagttctaaa 60
aacctaattc aaagttcttc catgatccta cactgcctcc aagatggtcc aggctggcat 120
aaggcctgag cggcggtgag atccgcggct gccagcagct tgtcgctctt cagctggtat 180
gaagcccctc ggccacccga gtctccagga cctgcccggg cgccgctcga aagggcgaat 240
t 241

<210> 358
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 358
aggtacgggg agtgggggtg aagcntgttc tctacatagg caacacagcc gcctaantca 60
caaagtcagt ggtcggccgc ttcgaccaac atgtggtgag cattccacgg gcgcatgaag 120
tctgggtgct gtgctcgagt ctctgaatat tttgatagga agcgacaaga aaattcaaac 180
tgctctttgc tgactactgg aaagtgaaaa gatgctcaag tttaccattc aaagaaacca 240
t 241

<210> 359
<211> 241
<212> DNA
<213> Homo sapiens

<400> 359
gaggtacaca aaaggaatac cttctgagag ccagggagtg aggaaagggg aaggagactt 60
gacgtcaagg gtgcttttga ggaacatgac gggccagcca gcctgcccca actttgaggc 120
cctgctgggc tcttgtgact ataaatatac tgtctatttc taatgcaatc cgtctttcct 180
gaaagatctt gttatctttt actattgaga catgctttca tttttgtggt cctgtttcca 240
a 241

<210> 360
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 360
ngtactctat actaattctg ccttttttata cttaattcta aatttctccc ctctaattta 60
caacaaattt tgtgattttt ataagaatct atgcctcccc aattctcaga ttcttctctt 120
ttctccttta tttctttgct taaattcagt ataagctttc ttggtatttt aggcttcatg 180
cacattctta ttcctaaaca ccagcagttc ttcagagacc taaaatccag tataggaata 240
a 241

<210> 361
<211> 241
<212> DNA
<213> Homo sapiens

<400> 361
aggtactctc cgtgccccga cactgaacat tatccagcca gatctgccca gtgccagctc 60
ccactttgta cttttcttac tatcctgtct agaatcatgt cttatgattt taacagatat 120
agaaccactc ctagaaaatg ttctttcact ttctcgtttc ctttttaatc tatcatcctg 180

actactgaac ttaaaatctt tttcttccct tttttgtttc tcttttcttt tatcctgttc 240
a 241

<210> 362
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 362
aggtactttt atacctngct tangtcagtg acagatttac caatgacaac acaattttaa 60
aattccaaca catatattac tttgtcctat gaagggcaaa aagtcaatat attttaaatt 120
ttaaaaacag aatggatata atgacctttt tacacatcag tgatatttaa aagacttaaa 180
gagacaatac tatggttgag acactggctt cctattccag ccctaattaa agaaaaaata 240
g 241

<210> 363
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 363
ttangtacta aaaacaaaat cctaattctg ttttaaagag ctgggagatg ttaatcatat 60
gctcagtttt tccacgttat aatttcctaa atgcaaactt ttcaatcagg gcagttcaaa 120
ttcattacat cacagtaaat aacagtagcc aactttgatt ttatgcttat aggaaaaaaa 180
atcctgtaga tataaaaaca gcaaattttg acaaataaaa ctcaaaccat tcatccctaa 240
a 241

<210> 364
<211> 241
<212> DNA
<213> Homo sapiens

<400> 364
ggtacaagca gttagtcctg aaggcccctg ataagaatgt catcttctcc ccactgagca 60
tctccaccgc cttggccttc ctgtctctgg gggcccataa taccaccctg acagagattc 120
tcaaaggcct caagttcaac ctcacggaga cttctgaggc agaaattcac cagagcttcc 180
agcacctcct gcgcaccctc aatcagtcca gcgatgagct gcagctgagt atgggaaatg 240
c 241

<210> 365
<211> 241
<212> DNA
<213> Homo sapiens

<400> 365
cgaggtactg agattacagg catgagccac cacgcccggc caaaaacatt taaaaaatga 60
ctgtccctgc tcaaatactg cagtaggaaa tgtaatttga catatatcac ttccagaaaa 120
aaactttaaa tctttctata aaatgaattt gatacatcat cagcatgaag tgaagttaaa 180
atctcttaca aagtaaattc aggtatatca acaatgagat ccaaaagtat cggttcaaga 240
t 241

<210> 366

<211> 241
<212> DNA
<213> Homo sapiens

<400> 366
ggcaggtaca catcaaacac ttcattgcct aaatgcaggg acatgcttcc atctgaccac 60
ttgactatcc gagcattgct ttctttaatt tcatttcctt cttcatctcg gcgtatcctc 120
catcttatag tattttctac ctttaatttt aacctggttc taccttcttc atccagcatt 180
tcttcatctt caaattcatc ttcataatac tgggctctac acttgagaaa gttgggcagt 240
t 241

<210> 367
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 367
gcaggtacaa ataattcctg ttgtnacatt tagtggacgc gattatctgt atacctcaaa 60
ttttaattta agaaagtatc acttaaagag catctcattt tctatagatt gaggcttaat 120
tactgaaaag tgactcaacc aaaaagcaca taacctttta aaggagctac acctaccgca 180
gaaagtcaga tgccctgtaa ataactttgg tctttcaaaa tagtggcaat gcttaagata 240
c 241

<210> 368
<211> 241
<212> DNA
<213> Homo sapiens

<400> 368
tttgtacatt gttaatagtg accctcggag gaaatggatt tctcttctat taaaaactct 60
atggtatata agcattacat aataatgcta cttaaccacc ttttgtctca agaattatca 120
ccaaagtttt ctggaaataa gtccacataa gaattaaata tttaaaaggt gaaatgttcc 180
ttattttaac tttagcaaga tcttttcttt ttcattaaga aacactttaa taattttaaa 240
g 241

<210> 369
<211> 241
<212> DNA
<213> Homo sapiens

<400> 369
gcaggtactt tattcttatt tcttatccta tattctgtgt tacagaaaaa ctactaccat 60
aaacaaaaca ccaaccagcc acagcagttg tgtcaagcat gacaattggt ctagtcttca 120
cattttatta gtaagtctat caagtaagag atgaagggtc tagaaaacta gacacaaagc 180
aaccagggtc caaatcacca aggtagatct gtgcttagct aaagggaaac acccgaagat 240
t 241

<210> 370
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 370
ngttcacagt gcccctccgg cctcgccatg aggctcttcc tgtcgctccc ggtcctggtg 60
gtggttctgt cgatcgtctt ggaaggccca gccccagccc aggggacccc agacgtctcc 120
agtgccttgg ataagctgaa ggagtttgga aacacactgg aggacaaggc tcgggaactc 180
atcagccgca tcaaacagag tgaactttct gccaagatgc gggagtggtt ttcagaagac 240
a 241

<210> 371
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 371
ggcaggtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc ttaggagtaa 60
aacaatatac tttacagggt gataataatc tccatagtta tttgaagtgg cttgaaaaag 120
gcaagattga cttttatgac attggataaa atctacaaat cagccctcga gttattcaat 180
gataactgac aaactaaatt atttccctag aaaggaagat gaaaggnagt ggagtgtggt 240
t 241

<210> 372
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 372
aggtacagca aagcgaccct tggtgnnata gatcagacgg aaattctctc ccgtcttgnc 60
aatgctgatg acatccatga atccagcagg gtaggttata tcagttcgga ccttgccatc 120
gattttaatg aaccgctgca tgcaaatctt ctttacttca tctcctgtca gggcatactt 180
aagtctgttc ctcaggaaaa tgatgagggg gagacactct ctcaacttgt ggggaccggt 240
g 241

<210> 373
<211> 241
<212> DNA
<213> Homo sapiens

<400> 373
tactgaaaca gaaaaaatgt attcccacaa aagctgttac acagcggttt cccgtcccca 60
gaagcagtag aaaatcttag cattccaatg gaaggcatgt atttgtaaaa tattctaaaa 120
tcagctctat agtttccttg tcctctttga taagggatca gacagagggt gtgtcccccc 180
tcagcagcta cccttcttga caaactggtc tccaataata cctttcagaa acttacaaga 240
c 241

<210> 374
<211> 241
<212> DNA
<213> Homo sapiens

<400> 374
caggtactaa aacttacaat aaatatcaga gaagccgtta gtttttacag catcgtctgc 60
ttaaaagcta agttgaccag gtgcataatt tcccatcagt ctgtccttgt agtaggcagg 120
gcaatttctg ttttcatgat cggaatactc aaatatatcc aaacatcttt ttaaaacttt 180

gatttatagc tcctagaaag ttatgttttt taatagtcac tctactctaa tcaggcctag 240
c 241

<210> 375
<211> 241
<212> DNA
<213> Homo sapiens

<400> 375
aggtacaaag gaccagtatc cctacctgaa gtctgtgtgt gagatggcag agaacggtgt 60
gaagaccatc acctccgtgg ccatgaccag tgctctgccc atcatccaga agctagagcc 120
gcaaattgca gttgccaata cctatgcctg taaggggcta gacaggattg aggagagact 180
gcctattctg aatcagccat caactcagat tgttgccaat gccaaaggcg ctgtgactgg 240
g 241

<210> 376
<211> 241
<212> DNA
<213> Homo sapiens

<400> 376
ggtacatttt actttccttc tttcagaatg ctaataaaaa acttttgttt atacttaaaa 60
aaaccataaa tcagacaaac aaaagaaacg attccaacat cacttctgtg atgagaaaag 120
aggcaatgga attcaacata agcaaagaaa actctacctg gaggaaagaa atcgatcagc 180
gaagaaacaa ctcggggctg ctgccagact gcaggccatg cgaggaggag cctcctagag 240
g 241

<210> 377
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 377
tcctttctgt ccaggtgatt cacagactag acctttctta tcctcctcct agagttttga 60
cttgggactc tagtgttaag atgatgagcc cgtgcatcag gtccttctgc actttggtgg 120
aagtctccca gggtaggttt cctatttgaa acagtggaat catgtttcca gtgataaagt 180
ttaatgacct catccttttt ttttttttc tcatctgcca tttgtgtgtc ttanatgggt 240
t 241

<210> 378
<211> 241
<212> DNA
<213> Homo sapiens

<400> 378
aggtcagcga tcaggtcctt tatgggcagc tgctgggcag ccccacaagc ccagggccag 60
ggcactatct ccgctgcgac tccactcagc ccctcttggc gggcctcacc cccagcccca 120
agtcctatga gaacctctgg ttccaggcca gcccccttggg gaccctggta accccagccc 180
caagccagga ggacgactgt gtctttgggc cactgctcaa cttccccctc ctgcagggga 240
t 241

<210> 379
<211> 241
<212> DNA
<213> Homo sapiens

<400> 379

tacggagcaa tcgaagaggc atatccacac ttggggtggc tatagggctg gaaaatgctg 60
aagatgactg ctttcactga ggtcaaggat tgtaatattg ccagctttgt aaagccatta 120
aagcagaagt ttcttcagtg atcttctctc taagaaacac catcacctcc atgtgcctta 180
cagaggcccc ctgcgttctg ctgcattgct tttgcgcaat cccttgatga tgaagatggt 240
c 241

<210> 380
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 380
acgtacacgc agaccgacat gggnnnttca ggcntnagat caaactcaaa acctgnaatg 60
atatccactc tctttttctt aagctcaggg aaatattcca agtagaagtc canaaagtca 120
tcggctaana tgcttcngaa tttgaattca tgcacatagg ccttgaaaaa actgtcaaac 180
tgannctgat cacccaccaa gtgggccntn tatgacacaa agcagaaacc tttctcntan 240
g 241

<210> 381
<211> 241
<212> DNA
<213> Homo sapiens

<400> 381
aggtacaact taatggatta gcttttgggt ttaactgaat atatgaagaa attgggtctg 60
tctaaagaga gggtatttca tatggctttt agttcacttg tttgtatttc atcttgattt 120
ttttctttgg aaaataaagc attctatttg gttcagattt ctcagatttg aaaaaggctc 180
tatctcagat gtagtaaatt atttcctttc agtttgtgaa agcaggattt gactctgaaa 240
g 241

<210> 382
<211> 241
<212> DNA
<213> Homo sapiens

<400> 382
gtactgctat aatcaatacg tctgatagac aggtttatcc actatattga ccctacctct 60
aaaaggattg tcataattta tatgctttat gtttacacct atgatacagt tgccttggaa 120
cacaaaattt ttcattgtaa ttaaaaaaag aagagttgtg cagacagaag aaatcaaatc 180
taagaaaatc acaggagtag ataaatactc tagaattcat atacccttgg aagatgggtt 240
t 241

<210> 383
<211> 241
<212> DNA
<213> Homo sapiens

<400> 383
ggcaggtaca aagtcttctc tttgcttttt ataattttaa agcaaataac acatttaact 60
gtatttaagt ctgtgcaaat aatccttcag aagaaatatc caagattctg tttgcagagg 120
tcattttgtc tctcaaagat gattaaatga gtttgtcttc agataaagtg ctcctgtcca 180
gcagaactca aaaggccttc aagctgttca gtaagtgtag ttcagataag actccgtcat 240
a 241

<210> 384
<211> 241
<212> DNA

<213> Homo sapiens

<400> 384
ggtacacaaa atacacttgc aagcttgctt acagagacct gttaaacaaa gaacagacag 60
attctataaa atcagttata tcaacatata aaggagtgtg attttcagtt tgtttttta 120
agtaaatatg accaaactga ctaaataaga aggcaaaaca aaaaattatg cttccttgac 180
aaggcctttg gagtaaacaa aatgctttaa ggctcctggt gaatggggtt gcaaggatga 240
a 241

<210> 385
<211> 241
<212> DNA
<213> Homo sapiens

<400> 385
ggcaggtcta caatggctct gtcccttctg tggaatcgtt acaccaagag gtctcagtcc 60
tggtccctga ccccacagtg agctgtttag atgatccttc acatcttcct gatcaactgg 120
aagacactcc aatcctcagt gaagactctc tggagccctt caactctctg gcaccaggta 180
ggtttggagg ctatgtccct ttaacttatc catgcagagt agccaaactt tacctgaaag 240
a 241

<210> 386
<211> 241
<212> DNA
<213> Homo sapiens

<400> 386
aggtaccttt ttcctctcca aaggaacagt ttctaaagtt ttctgggggg aaaaaaaact 60
tacatcaaat ttaaaccata tgttaaactg catattagtt gtgttacacc aaaaaattgc 120
ctcagctgat ctacacaagt ttcaaagtca ttaatgcttg atataaattt actcaacatt 180
aaattatctt aaattattaa ttaaaaaaaa aactttctaa gggaaaaata aacaaatgta 240
g 241

<210> 387
<211> 241
<212> DNA
<213> Homo sapiens

<400> 387
accccactgg ccgctgtgga gtatctccac tctcccctcg tgagggccgc tcccaccgac 60
cagtcgaact ttcgtaaatg gagttaatgt gtttccactc ccctttccc ctttctggcc 120
ttttggtcca gaatttcctg gccttccggc atatcctggg agtcctcgac ttccaggaaa 180
gccaattgct ccccgatcac ctttaagacc cggaggacct attggacctg gaaatcctcg 240
t 241

<210> 388
<211> 241
<212> DNA
<213> Homo sapiens

<400> 388
tttgtactct tgtccacagc agagacattg agtataccat tggcatcaat gtcaaaagtg 60
acttcaatct gaggaacacc tcggggtgca ggaggtatgc ctgtgagttc aaacttgcca 120
agcaggttgt tatcctttgt catggcacgc tcgccttcat aaacctgaat aagtacacca 180
ggctggttgt cagaataggt agtgaaggtc tgtgtctgct tggtaggaat ggtggtatta 240
c 241

<210> 389
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 389
tacctntgtt agtgagcacc ttgtcttntg tgcttatntc ttnaagataa atacatggaa 60
ggatgtgaaa atcggaacac caactatgtg tctcactgca tctaagtgaa gcagccacag 120
ctgtgagagt tttcaaagca gaaagatgct gatgtgacct ctggaattca gacatactga 180
gctatgggtc agaagtgttt tacttaaaaa gcaaacaatc cccaggaaat actgaatagg 240
a 241

<210> 390
<211> 241
<212> DNA
<213> Homo sapiens

<400> 390
gcaggtacat ccacatgttc ctccaaatga cgtttggggt cctgcttgcc aacattcttt 60
attgccagct gttcaggtgt catcttatct tcttcttcta cagccttatt gtaattcttg 120
gctaattcca acatctcttt taccactgat tcattgcgtt tacaatgttc actgtagtcc 180
tgaagtgtca aaccttccat ccaactcttc ttatgcaaat ttagcaacat cttctgttcc 240
a 241

<210> 391
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 391
cnggcacaan cttntgtttt tnntnttttt ttttttttn tctttatttn tttttantnt 60
taaanaaaaa nnntannnaa annnggttt aaatnctntn nncagancat taaaactgaa 120
ggggaaaaaa aaaccaaaaa cgagcttntt anttnacntg ggnttgggnn gntgctgatn 180
tnaagaagca annttanan cnngcnnnat ganngagngn tcannttgaa atttnnaccc 240
t 241

<210> 392
<211> 241
<212> DNA
<213> Homo sapiens

<400> 392
gaggtactaa atggtatcct tagattaaaa ttttgtgctt gataacagct gtttttttcta 60
cattagaaat aagatgccac acaaggaact acattccaga tttaaagaaa tgaaaggata 120
ccattagtgt gtataacaga ttattgttca tacttgtaaa gcatcttatg tcattgagaa 180
tataaagaac agtgccttag aagacagtga aaggtaagct ctagcttaat gtctatgatt 240
t 241

<210> 393
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 393
ggcaggtaca taagcataat cagttatgga cagcttcttg tataaattgc tattcancaa 60
tacataaact gcctnaaaga tttatgctta caggtagaca ttcaatttac caataaaaca 120
gcatgttctg aaaatatggg cacattttaa aacatattaa gacagttctg ttaaccataa 180
tagtcccaca gtatgactga gtaataagaa tctacttcaa aagnaaaaaa aaaattaatc 240
a 241

<210> 394
<211> 241
<212> DNA
<213> Homo sapiens

<400> 394
aggtacagca gcagtagatg gctgcaacaa ccttcctcct accccagccc agaaaatatt 60
tctgccccac cccaggatcc gggaccaaaa taaagagcaa gcaggccccc ttcactgagg 120
tgctgggtag ggctcagtgc cacattactg tgctttgaga aagaggaagg ggatttgttt 180
ggcactttaa aaatagagga gtaagcagga ctggagaggc cagagaagat accaaaattg 240
g 241

<210> 395
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 395
nggcnggnnc caanatatga aatntnanta tnatacatga tnaaaagctt tatntatttt 60
agtgagtaat taagtttaca ctgtgaataa ggattaattc ccagatgacc atctacagtt 120
actaccacat agagggtata cacggatgga tcgattacaa gaatataaaa cttattttcc 180
ttcctgtatc cacatttctt tgcaatgtga atttgcaggc cctctcaaga agtggagtct 240
a 241

<210> 396
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 396
gaggtacacc ttgaatgaca atgctnggag ccccccctgtg gtcatcgacg cctccactgc 60
cattgatgca ccatccaacc tgcgtttcct ggccaccaca cccaattcct tgctggtatc 120
atggcagccg ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc 180
tcctcccaga gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg 240
c 241

<210> 397
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)

<223> n = A,T,C or G

<400> 397
ggcaggtacc agcaggggga tgtgtttctg gggaattgtg gctctggaag cttcacggtt 60
tcccagaatg tggaaaatat atctgtgcan gatagaaatc ctgcccagag gctgtttctg 120
tctcatttga gctctccttc atgtggcaga gctgactgtg gcggtttagg agcctacatt 180
ttagaaaagc ttacctcaaa gttctgcatt gagcctgagc actggaaagg agataaaata 240
a 241

<210> 398
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 398
gangtgacca ngacatcacc tnacacntgg aaagcganga nttgaatggt gcntacaang 60
ccntacccnt tgcccannac ctgaacgcgc cttntgattg ggacagccgt gggaaggaca 120
gttatgaaac nantcanctg gatgaccana gtgntgaaac cnacanncac angcnntcna 180
cattatataa ncggaaagct aatgatgaga gcaatgatca ttccgatgtn attgatagtc 240
a 241

<210> 399
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 399
cagagtgaga tgggagtggg agggccaatc tgatacagaa gggggtgaag ggtagggccc 60
ctgagcagcc cacccttac cctgacgaag gcaatcctcc tctggaatgt ctcttccctc 120
ttcagtctgg gttctgcctc agccacgaac tgggaaggag tgaggaacat cccaacggca 180
atgagagtat cccagtgact ccaaacagga angaatcagt gttcanaaag tcagggccct 240
t 241

<210> 400
<211> 241
<212> DNA
<213> Homo sapiens

<400> 400
ggtactcttg ctcttttagc tagagtgtat gtgaaaataa agaaatacat cattgtattc 60
acaaccatgt gtcttcattt ataacttttt gtttaaaaaa tttttagttc aagtttagtt 120
cattgatatt atcctctgaa tgcagttaag gctgggcaga aattctactc atgtgacatc 180
tgccacaggt ctattttgaa gcttttcttc taatgggcaa tgtttgtcct taccaggatt 240
t 241

<210> 401
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> (1)...(241)
<223> n = A,T,C or G

<400> 401
nncaggtact ttgtagagca gagagaggct ttggttcctc ctttcttcaa tcacgtggag 60
atgtgtcatc acctgggatt tcatctgggc cgccttttct gggtcaacag ccaacacatg 120
ctggtaatga cggatggtat gtaagcgatc tttgttctca gcacggacat aacgccgtaa 180
ggcctggaga atgcgatgag gccgtggcgg gtcagactgc aaggcagcca ggtagttctc 240
c 241

<210> 402
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 402
ggcaggtcca aaaaaaacct aaaaannngtt tcaggaatgt agagaaatat ccaacttaaa 60
tagcgaaaaa gtgcaccata attactgctg cactgcagtc atttctgcaa ttcccatgtt 120
tcttaaataa ctatcttgtc agataacaca caatataaag agcaattatg aaaaacagac 180
atttacatat acttctaaag tcttattggg aatatcctgt ttggccattg ggataaccaa 240
t 241

<210> 403
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 403
aggtgttaac tacccgctcc gagacgggat tgatgacgag tcctatgang ccattttcaa 60
gccggtcatg tccaaagtaa tggagatgtt ccagcctagt gcggtggtct tacagtgtgg 120
ctcagactcc ctatctgggg atcggttagg ttgcttcaat ctaactatca aaggacacgc 180
caagtgtgtg gaatttgtca agagctttaa cctgcctatg ctgatgctgg gaggcggtgg 240
t 241

<210> 404
<211> 241
<212> DNA
<213> Homo sapiens

<400> 404
caggtactgc aacccataaa atactgtttc ctcatatttc accttcctta atttggagtt 60
ttctgtcttc ttttcacggc attcaaagta ggaataaact ttgcttgtgt tgggtggata 120
ttgtttatag tgagtaacct tgtaggagtc ggtggccagg aggatgttga actcggcttc 180
tgccgcagga ttcatctcgg gccggaggac aaggggcccg cgcgccgcga gctccctgac 240
c 241

<210> 405
<211> 266
<212> DNA
<213> Homo sapiens

<400> 405

ttctgggctg gggagtggag agaaagaagt tgcagggctt acaggaaatc ccagagcctg 60
aggttttctc ccagatttga gaactctaga ttctgcatca ttatctttga gtctatattc 120
tcttgggctg taagaagatg aggaatgtaa taggtctgcc ccaagccttt catgccttct 180
gtaccaagct tgtttccttg tgcatccttc ccaggctctg gctgcccctt attggagaat 240
gtgatttcca agacaatcaa tccaca 266

<210> 406
<211> 231
<212> DNA
<213> Homo sapiens

<400> 406
ttggtgaaga accattcctc ggcatccttg cggttcttct ctgccatctt ctcatactgg 60
tcacgcatct cgttcagaat gcggctcagg tccacgccag gtgcagcgtc catctccaca 120
ttgacatctc cacccacctg gcctctcagg gcattcatct cctcctcgtg gttcttcttc 180
aggtaggcca gctcctcctt caggctctca atctgcatct ccaggtcagc t 231

<210> 407
<211> 266
<212> DNA
<213> Homo sapiens

<400> 407
cagcatcatt gtttataatc agaaactctg gtccttctgt ctggtggcac ttagagtctt 60
ttgtgccata atgcagcagt atggagggag gattttatgg agaaatgggg atagtcttca 120
tgaccacaaa taaataaagg aaaactaagc tgcattgtgg gttttgaaaa ggttattata 180
cttcttaaca attcttttt tcagggactt ttctagctgt atgactgtta cttgaccttc 240
tttgaaaagc attcccaaaa tgctct 266

<210> 408
<211> 261
<212> DNA
<213> Homo sapiens

<400> 408
ctgtgtcagc gagcctcggt acactgattt ccgatcaaaa gaatcatcat ctttaccttg 60
acttttcagg gaattactga actttcttct cagaagatag ggcacagcca ttgccttggc 120
ctcacttgaa gggtctgcat ttgggtcctc tggtctcttg ccaagtttcc cagccactcg 180
agggagtaat atctggaggg caaagaagag acttatgtta ttgttgaacc tccagccaca 240
gggaggagca tgggcatggg t 261

<210> 409
<211> 266
<212> DNA
<213> Homo sapiens

<400> 409
gctgacagta atacactgcc acatcttcag cctgcaggct gctgatggtg agagtgaaat 60
ctgtcccaga cccgctgcca ctgaatcggt cagggatccc ggattcccgg gtagatgccc 120
agtaaatgag cagtttagga ggctgtcctg gtttctgctg gtaccaagct aagtagttct 180
tattgttgga gctgtctaaa acactctggc tggtcttgca gttgatggtg gccctctcgc 240
ccagagacac agccagggag tgtgga 266

<210> 410
<211> 181
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 410
caaaaggtnc tttttgntca aaancnattt ttattccttg atatttttct ttttttttt 60
tttgnggatg gggacttgtg aatttttcta aaggggnnnn ttnannnngg aagaaaaccn 120
ngntccggtt ccagccaaac cngtngctna ctttccacct tntttccacc tccctcnggt 180
t 181

<210> 411
<211> 261
<212> DNA
<213> Homo sapiens

<400> 411
gcccctgcag tacttggccg atgtggacac ctctgatgag gaaagcatcc gggctcacgt 60
gatggcctcc caccattcca agcggagagg ccgggcgtct tctgagagtc agggtctagg 120
tgctggagtg cgcacggagg ccgatgtaga ggaggaggcc ctgaggagga agctggagga 180
gctggccagc aacgtcagtg accaggagac ctcgtccgag gaggaggaag ccaaggacga 240
aaaggcagag cccaacaggg a 261

<210> 412
<211> 171
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 412
nttttntctt tacaattcag tcttcaacaa cttgagagct ttcttcatgt tgncaagcaa 60
cagagctgta tctgcaggnt cgtaagcata nagacngttt gaatatcttc cagngatatc 120
ggctctaact gncagagatg ggtcaacaaa cataatcctg gggacatact g 171

<210> 413
<211> 266
<212> DNA
<213> Homo sapiens

<400> 413
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atttttataa agtactgtaa ttctttcatt gaggggctat gtgatggaga cagactaact 120
cattttgtta tttgcattaa aattattttg ggtctctgtt caaatgagtt tggagaatgc 180
ttgacttgtt ggtctgtgta aatgtgtata tatatatacc tgaatacagg aacatcggag 240
acctattcac tcccacacac tctgct 266

<210> 414
<211> 266
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 414
tttgccataa ttgagtgaaa agtggcagat ggcattaact ctgctccgct tcaagctggc 60
tccatgacca ctcaaggcct ccccancctg ttcgtcaagt tgtcctcaag tccaagcaat 120
ggaatccatg tgtttgcaaa aaaagtgtgc tantttaag gnctttcgta taagaatnaa 180
tganacaatt ttcctaccaa aggangaaca aaaggataaa tataatacaa aatatatgta 240
tatggttgtt tgacaaatta tataac 266

<210> 415
<211> 266
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G

<400> 415
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gtttgcgcaa cgttgttgcc attgctacag gcatcgtggt gtnacgctcg tcgattggta 120
tggcttcatt cagctccggt tcccaacgat caaggcgagt tacatgatcc cccatgttgt 180
gcaaaaaagc ggttagctcc ttcggtcctc cgatcgttgt canaagtaag ttggccgcag 240
tgttatcact catggttatg ngcagca 266

<210> 416
<211> 878
<212> DNA
<213> Homo sapiens

<400> 416
cctgacgata gccatggctg taccacttaa ctatgattct attccaactg ttcagaatca 60
tatcacaaaa tgacttgtac acagtagttt acaacgactc ccaagagagg aaaaaaaaaa 120
aaaaagacgc ctcaaaattc actcaacttt tgagacagca atggcaatag gcagcagaga 180
agctatgctg caactgaggg cacatatcat tgaagatgtc acaggagttt aagagacagg 240
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acaaagggct ctgaaggagg tgttctccaa gcaacaagga gactgcttca gtacaagact 480
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cacagcagcc ctttttggct gcttccacaa tagatacttt atggagtggc acagccaacc 780
ctatctgtga cctgccctgc ggataaacac agccaagcag gtttaattag atcaaagaca 840
caaagggcta ttccctcctt tcataacaac gcagacct 878

<210> 417
<211> 514
<212> DNA
<213> Homo sapiens

<400> 417
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cacccagcgg gaggtgggat gtgagacagc ccacattgga aaatccagaa aaccgggaac 180
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accagggtcc aggactaagg cgttttctcc atagcctcaa cattttggga atcttccctt 420
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ttttgtgctt tgatgccagg aatgccgcct agtt 514

<210> 418
<211> 352
<212> DNA
<213> Homo sapiens

<400> 418

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agtaggctca ggatctgctg aaggtcggag gagttagtcc ccgcaatcaa gagcctgtct 180
tcctgaagcc cttggtgata ttttgccact cagccaagaa tgaggatgca tccttcagat 240
tctctatgtc ccgaacctgg aacccatcca cgccagcttg cagccaaaac tccagagcat 300
ccttcacctt ggtggaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 352

<210> 419
<211> 344
<212> DNA
<213> Homo sapiens

<400> 419
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attgagactc aaaggcttat actggcgtct gaaactatgt ccttcgttaa acccgtattt 180
tgggattcgg atgtaaaatg gagtctggcc tccctcaaag cccaagcggg gccgggttcc 240
tctttgcctt tctcctttat ggcctctgcc acattttcta cctcttctcc gacctcttgg 300
tcttctctcc ggtttcttgg agccgggatt cggctttaag ttgg 344

<210> 420
<211> 935
<212> DNA
<213> Homo sapiens

<400> 420
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cgaggttctc aaagatccaa aggagggaaa gggtattgga aacactgtgt atcatctgag 180
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tgctgcttct gccccctggg acccagcaca ttgttagacc atcttcttga ctgaaaattc 420
tctcctgatg ctgagccctg caccaccacc ttccttttcc taactatgaa ttgatggcaa 480
agtccactca aaacaaccag ttaagtgctc acgagagagt agtcaagcac ctccagaaag 540
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tggcaattct gagtgacttg cgcttgtctt atggtgtggt caagggacgt tcagaactac 780
ggaaaacttt tactgaaaca gcgaagcaga gtataccggc atgagaggga agatgaacac 840
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agtaaaaaaa ctgaaatcgc aagtcaaaaa atcca 935

<210> 421
<211> 745
<212> DNA
<213> Homo sapiens

<400> 421
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ggttaacaac agtcccctgc ttggcttcta ttctgaatcc ttttctttca ccatggggtg 180
cctgaagggt ggctgatgca tatggtacaa tggcacccag tgtaaagcag ctacaattag 240
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ccacgaccat ggttgtcatc cattacttga tcctacttta catgtctagt ctgtgtggtt 420
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ggacttttag caagcgggct cactggaaga gactgaacct ggcatggaat tcctgaagat 540
gtttggggtt tttttctttc ttaatcgaaa gttaacattg tctgaaaagt tttgttagaa 600
ctactgcgga acctcaaaat cagtagattt ggaagtgatt caaagctaaa ctttttcctt 660
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tttgcttctt tgttagttgt cagac 745

<210> 422
<211> 764
<212> DNA
<213> Homo sapiens

<400> 422
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gatggcaaag gtggtggtgc tttcatcttc aggcagaagc ctctgcccat ccccctcaag 120
ggctgcaggc ccagttctca tgctgccctt gggtgggcat ctgttaacag aggagaacgt 180
ctgggtggcg gcagcagctt tgctctgagt gcctacaaag ctaatgcttg gtgctagaaa 240
catcatcatt attaaacttc agaaaagcag cagccatgtt cagtcaggct catgctgcct 300
cactgcttaa gtgcctgcag gagccgcctg ccaagctccc cttcctacac ctggcacact 360
ggggtctgca caaggctttg tcaaccaaag acagcttccc ccttttgatt gcctgtagac 420
tttggagcca agaaacactc tgtgtgactc tacacacact tcaggtggtt tgtgcttcaa 480
agtcattgat gcaacttgaa aggaaacagt ttaatggtgg aaatgaacta ccatttataa 540
cttctgtttt tttattgaga aaatgattca cgaattccaa atcagattgc caggaagaaa 600
taggacgtga cggtactggg ccctgtgatt ctcccagccc ttgcagtccg ctaggtgaga 660
ggaaaagctc tttacttccg cccctggcag ggacttctgg gttatgggag aaaccagaga 720
tgggaatgag gaaaatatga actacagcag aagcccctgg gcag 764

<210> 423
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 423
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caggatgtct gacttcaaat tgaaactccc aaagtaatga gtttggaagg gtggggtgtg 120
gcctttccag gatgggggtc ttttctgctc ccagcggata gtgaaacccc tgtctgcacc 180
tggttgggcg tgttgctttc ccaaaggttt ttttttagg tccgtcgctg tcttgtggat 240
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cggcaacctg cacctgttca tcaatgccta caacaggtat tgggatgtag ttcagccaca 480
tcattgctat ttatgaggtg tcttctgtag atccgaaatg tgggacagat gagagggaga 540
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gatctgaaca aacactccag accactgggg gtgcagacgt gagagggacg cagtcgcaca 720
ctcagagggt tgagagtaaa tatgtgtgcc cgctgctgac cttcacgaaa ggccaaatgt 780
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gcttctggga gtttgtcatt ccaaggataa ggaggacctg aacatggcct ttgcctaagg 900
cgtggccctc tcaaccagca ctaggtgctt atctggagct cagctagggg aggagacagc 960
tcagggccat tggtgtcagc cagagactct gtaatcttcc agggagctcg ctcaacctgc 1020
tgagctcgct ctgccacgca c 1041

<210> 424
<211> 1288
<212> DNA
<213> Homo sapiens

<400> 424
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ggacccaagc gaaaaaggta tctcaagact aacggccgga atctggaggc ccatgaccca 180
gaacccagga aggatagaag cttgaagacc tggggaaatc ccaagatgag aaccctaaac 240
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cagtattatg cctgggccag tcttgagcca gctttaaatc acagctttta cctatttgtt 420
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ccaaaatcca gtcagtatct aatctggctt ttgttaactt ccctcaggag cagacattca 540
tataggtgat actgtatttc agtcctttct tttgacccca gaagccctag actgagaaga 600

taaaatggtc aggttgttgg ggaaaaaaaa gtgccaggct ctctagagaa aaatgtgaag 660
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agaagcacct gccagcaaca gcttccttct ttgagcttag tccatccctc atgaaaaatg 780
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tctttgctgt ttggaagatt gaaaaatatt gttcagcatg ggtgaccacc agaaagtaat 1200
cttaagccat ctagatgtca caattgaaac aaactgggga gttggttgct attgtaaaat 1260
aaaatatact gttttgaaaa aaaaaaac 1288

<210> 425
<211> 446
<212> DNA
<213> Homo sapiens

<400> 425
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gcctaacatc ttccacaagg atcccgatgt gaacatgctg cacgtgtttg ttctgggcga 120
atggcagccc atcgagtacg gcaagaagaa gctgaaatac ctgccctaca atcaccagca 180
cgaatacttc ttcctgattg ggccgccgct gctcatcccc atgtatttcc agtaccagat 240
catcatgacc atgatcgtcc ataagaactg ggtggacctg gcctgggccg tcagctacta 300
catccggttc ttcatcacct acatcccttt ctacggcatc ctgggagccc tccttttcct 360
caacttcatc aggttcctgg agagccactg gtttgtgtgg gtcacacaga tgaatcacat 420
cgtcatggag attgaccagg aggacc 446

<210> 426
<211> 874
<212> DNA
<213> Homo sapiens

<400> 426
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tacagccatg ctgtttcaga agacttgaaa tgccattgat agtttaaaaa ctctacaccc 180
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tggtgatgga taaattcaga aatgcttccc caaaggtggg tggttttaa aaagttttca 360
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caagagggtc ctttggactg gatagggagc acttgggagc tgtacaccat cagtcataat 540
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cctcgtaatg gcaaaactcc ccaaatgaca cccaggacca cagcaatgat ctgtcggaac 780
cagtagatca catctaaaaa ttcatcctta tcctcccagg ccgcgtcgct ccgcagcacc 840
ttactccaga cggagacttt gagggccccg ttgg 874

<210> 427
<211> 638
<212> DNA
<213> Homo sapiens

<400> 427
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ataatttaag ttgctatcag ctgatattag tagctttgca accctgatag agtaaataaa 240
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tgcaaaaaca agatgtttgt agctgtttca gagagagt 638

<210> 428
<211> 535
<212> DNA
<213> Homo sapiens

<400> 428
acaagatgat tcttcctcct caatttgaca gatcaaagaa gtatcccttg ctaattcaag 60
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caactgtgat ggcaagagca gaatatttca gaaatgtaga ctatcttctc atcca 535

<210> 429
<211> 675
<212> DNA
<213> Homo sapiens

<400> 429
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aaatacatag ttttcaataa ataatgctta attttacaac tttgatacag caatgtcata 180
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acccacaaca tatgt 675

<210> 430
<211> 434
<212> DNA
<213> Homo sapiens

<400> 430
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gagccacctt gtccattgcc agggacttgg tggtgcaggt ctgtgttact cctgagagct 180
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cacctgggac agtcatctca aagtcggtgc ctacgaggct gctgagatac tccttgtgcc 360
ggccataaag atccttgaac actcgccgtt cccgctcctc ctcctccggc tgtgcgtggg 420
gggaaacatt gtcg 434

<210> 431
<211> 581
<212> DNA
<213> Homo sapiens

<400> 431
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ggccacgagt atccagctcc aagcccaagt gaggcgggga gtcaacttcc ccatgattgc 120
caagtgacca agaccagaag cagggacgat taggctagtt ctgcggcaag gtgaactgga 180
gaccctgtct ctgccctcct tccctggcct gtcccacaga catcccgttg tttaacccac 240
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tcagtagaag gctcattagt gtgaaggagt gagaggccag gccttcctgt gacataatgc 420
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caagcaccac tggatggctc tggagccagg ggacttctat gcacatacaa ccaacatcac 540
cccactctgc tcatctgtgc ctccaccctg aacagcagag t 581

<210> 432
<211> 532
<212> DNA
<213> Homo sapiens

<400> 432
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ctgcataact ggaagaagag attcttcagt atatgacagg taatgttgta gagttggtgt 240
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agtatgttgc tcgacatcaa cctctccaat cttagatgct ctccgaagga agtgcaaagg 420
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<210> 433
<211> 531
<212> DNA
<213> Homo sapiens

<400> 433
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tgaaatgact tcttaaatat ttagttgata gactgctaca ggtaataggg acttagcaag 180
ctcttttata tgctaaagga gcatctatca gattaagtta gaacatttgc tgtcagccac 240
atattgagat gacactaggt gcaatagcag ggatagattt tgttggtgag tagtctcatg 300
ccttgagatc tgtggtggtc ttcaaaatgg tggccagcca gatcaaggat gtagtatctc 360
atagttccca ggtgatattt ttcttattag aaaaatatta taactcattt gttgtttgac 420
acttatagat tgaaatttcc taatttattc taaattttaa gtggttcttt ggttccagtg 480
ctttatgttg ttgttgtttt tggatggtgt tacatattat atgttctaga a 531

<210> 434
<211> 530
<212> DNA
<213> Homo sapiens

<400> 434
acaagagaaa acccctaaaa aaaggatggc tttagatgac aagctctacc agagagactt 60
agaagttgca ctagctttat cagtgaagga acttccaaca gtcaccacta atgtgcagaa 120
ctctcaagat aaaagcattg aaaaacatgg cagtagtaaa atagaaacaa tgaataagtc 180
tcctcatatc tctaattgca gtgtagccag tgattattta gatttggata agattactgt 240
ggaagatgat gttggtggtg ttcaagggaa aagaaaagca gcatctaaag ctgcagcaca 300
gcagaggaag attcttctgg aaggcagtga tggtgatagt gctaatgaca ctgaaccaga 360
ctttgcacct ggtgaagatt ctgaggatga ttctgatttt tgtgagagtg aggataatga 420
cgaagacttc tctatgagaa aaagtaaagt taaagaaatt aaaaagaaag aagtgaaggt 480
aaaatcccca gtagaaaaga aagagaagaa atctaaatcc aaatgtaatg 530

<210> 435
<211> 677

<212> DNA
<213> Homo sapiens

<400> 435
accttatgat ctaattaata gatattagaa acagtagaaa gacaagttac acgtcaatgc 60
ccaatgacta gagtcaacat taaagagttg taatttaagt aatccaaact gacatctaat 120
tccaaaatca tttataaaat gtatttggct ttggaatcca caggacttca aacaagcaaa 180
gtttcactgc agatagtcac aaagatgcag atacactgaa atacttaaga gccttattaa 240
tgatttttgt tattttggat cttctgtttt tttcttatta tggtccgaag cctccttaat 300
accaatttat cagacagaag catgtcatct tgttgttcaa gataatccag taaattttca 360
gtccattcaa gtgccgcttt atggctaata cgcttctctg gattcagttc tgtttttcta 420
ctcttactgg aaggcttttg ctcagcagcc ttggtctggt cctcagcact ttcactgtca 480
gtcagcacct gacagcttga gtcactgctc cgagagtcga accactgatc aatattctca 540
atgtcaacat gttcacattc ttctgtgttc tgtaaaactg ttgctaaatt agctgctaaa 600
atggctcctt catcaatgtt catacctgaa ttctcttcat tgccagggaa aagtttttc 660
catgctttgg ttatggt 677

<210> 436
<211> 573
<212> DNA
<213> Homo sapiens

<400> 436
acctcttagg gtgggagaaa tggtgaagag ttgttcctac aacttgctaa cctagtggac 60
agggtagtag attagcatca tccggataga tgtgaagagg acggctgttt ggataataat 120
taaggataaa atttggccag ttgacagatt ctgtttccag cagtttttac agcaacagtg 180
gagtgcttca gtattgtgtt cctgtaaatt taattttgat ccgcaatcat ttggtataca 240
atgctgtttg aagttttgtc ctattggaaa agtcttgtgt tgcaggggtg cagttaagat 300
ctttgtgatg aggaatggga tgggctaatt ttttgccgtt ttcttggaat tgggggcatg 360
gcaaatacag tagggtagtt tagttcttta cacagaacat gataaactac acctgttgat 420
gtcaccgtct gtcaatgaat attatagaag gtatgaaggt gtaattacca taataacaaa 480
acaccctgtc tttagggctg acctttcgtc ctttgacctc ctcagcctcc attcccatct 540
tcgctcagac tgcaagtatg tttgtattaa tgt 573

<210> 437
<211> 645
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(645)
<223> n = A,T,C or G

<400> 437
acaattggta tccatatctt gttgaaattg taatgggaaa acaatatatt tcaatctcta 60
tgtagatagt gggtttttgt tttcataata tattctttta gtttactgta tgagttttgc 120
aggactgcat aatagatcac cacaatcata acatcttagg accacagaca tttatgagat 180
catggcttct gtgggttaga agtatgctca tgtcttaact gggtcctctg ctcagtctta 240
tctggctgca atcaaggtgt cagctgggct gaattttcat ttggaatctt gactgggaaa 300
gagtctgctt ccaaggtcat gaagtttgct ggcaaaatgt atgttttat gacagtatga 360
ctgaaatccc aagctatctc ctgactttta gctgggtaat ctcaggccct aaatgttgcc 420
tacagttcct agaggctggt cacagttctt agccatgtgg atttcctcaa catggctgct 480
tgcttcatca agtcagcaag aatagcctgt catatcagtg tatatcaggc tcactcagga 540
taatttccct actgatgagc caaacactaa ctgattttag agcttaacta catctgcaaa 600
attcngttca ccagaggcaa gtcatattca gggaaggaga agtgt 645

<210> 438
<211> 485
<212> DNA
<213> Homo sapiens

<400> 438
acagaattga gagacaagat tgcttgtaat ggagatgctt ctagctctca gataatacat 60
atttctgatg aaaatgaagg aaaagaaatg tgtgttctgc gaatgactcg agctagacgt 120
tcccaggtag aacagcagca gctcatcact gttgaaaagg ctttggcaat tctttctcag 180
cctacaccct cacttgttgt ggatcatgag cgattaaaaa atcttttgaa gactgttgtt 240
aaaaaaagtc aaaactacaa catatttcag ttggaaaatt tgtatgcagt aatcagccaa 300
tgtatttatc ggcatcgcaa ggaccatgat aaaacatcac ttattcagaa aatggagcaa 360
gaggtagaaa acttcagttg ttccagatga tgatgtcatg gtatcgagta ttctttatat 420
tcagttccta tttaagtcat ttttgtcatg tccgcctaat tgatgtagta tgaaaccctg 480
catct 485

<210> 439
<211> 533
<212> DNA
<213> Homo sapiens

<400> 439
acagcagttt cctcatccct gcagctgtgt ttgaacaggt catttaccat actgtcctcc 60
aggttcaaca gtatggctcc aaatgatgaa atttcattct gattttctgg ctgaagacta 120
ttctgtttgt gtatgtccac cacagttact ttatcccttc atctgtggat gggcagaatg 180
aaacatatat ggaaatgttc tgtgcaataa aaacagcagt ggtaacacag atgtaggctc 240
tgagtgtctc actggagact gaagtccaca gatatgcaac aaagcctttg tctccctgat 300
gtttttgcct cctgctggtc atgtgctttc acacatcaag agaggacatt taacatttga 360
gccacagtgt catttgctgt tgtctgatgg ttggttggca gagaatttga actggagatg 420
aactttatta tccaggacgc tgagagtata acatgcatga cagagctttt agagcactgt 480
gatgtaacat gtcaagcaga aatagggagc atgtttacag ccattctatg aaa 533

<210> 440
<211> 341
<212> DNA
<213> Homo sapiens

<400> 440
catggggtag gggggtcggg gattcattga attgtggttg gcaggagcaa gccctgctca 60
cactctcaca ctcgcaccca gaattgtcaa agatacagat tgtaaaaatc tacgatccct 120
cagtctcact cacaaaaaat aaaatctcat gtccccaacg aacccagagt cagacgacag 180
ctggagcatt ggcagggaca gtcagaaagg agacaagtga aaacggtcag atggacacag 240
gcggaggaga aaagacagag ggagagagac catcgggaac aatcagaggg gccgagacga 300
tcagaaaagg gtcagcccga gacaggctga gccagagttt c 341

<210> 441
<211> 572
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(572)
<223> n = A,T,C or G

<400> 441
aagtttgggg ataatttatt atgcagcaag agataataca caggacttct canagcactt 60
aatatgttaa tataaatctc caanaaaaaa gatatacaat gaaacattcc tcttagttat 120
ctggccaagg anactttntt tttttganaa tattcttcaa aaagctgatc taatgatatg 180
gctctggtcc tacaattcca tgtaacttct aaccttgatt ttatctcatg agcaaatcat 240
ttatccttcc agaacctcaa cttttccctt ttacaaagta gaaataaacc atctgccttt 300
acataaatca ttaatacagc cctggatggg cagattctga gctatttttg gctggggggt 360
gggaaatagc ctgtggaggt cctaaaaaga tctacggggc tcgagatggt tctctgcaag 420
gtagcaggtg ggctcagggc ccatttcagt ctttgttccc caggccattt ccacaaaatg 480
gtgagaaata gtgtcttctt ttagcttgct cataactcaa agatgggggg catggacctg 540
ggcctttcta ggctagggca tgaacctcct cc 572

<210> 442
<211> 379
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(379)
<223> n = A,T,C or G

<400> 442
tcccagctgc actgcttaca cgtcttcctt cgtnttcacc taccccgagg ctgactcctt 60
ccccagntgt gcagctgccc accgcaaggg cagcagcagc aatgagcctt cctctgactc 120
gctcagctca cccacgctgc tggccctgtg agggggcagg gaaggggagg cagccggcac 180
ccacaagtgc cactgcccga gctggtgcat tacagagagg agaaacacat cttccctaga 240
gggttcctgt agacctaggg aggaccttat ctgtgcgtga aacacaccag gctgtgggcc 300
tcaaggactt gaaagcatcc atgtgtggac tcaagtcctt acctcttccg gagatgtagc 360
aaaacgcatg gagtgtgta 379

<210> 443
<211> 511
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 443
acatgccccc aaaggctcgc ttcattgcta cgattctcta cttaaatcca cattcacagc 60
tattgcctca gaccctctgg aggaggggcc aggggttagc tggctttgaa tagcatgtag 120
agcacaggca gtgtggccac aaatgtcaca caggtgacca gggtgctata gatggtgttc 180
ctgttgactt gggcttctag tctctgctcc gtgtctgaca gtgccaagat catgctcccc 240
tgctccagca agaagctggg catagccccg tctgctggtt ccaccaggcc tgggtgtgct 300
gcagacttta caagctgaac caccccagcc atttggctac aagtcttttc taggccatca 360
agctgctctc gtaagccttc tagacatgaa tggacttgcc tggaatgact aagctgctct 420
ttcaaggcag ctgaaaggac atcnacatct ctgtctctgg tcgggggact acctgcctgt 480
gacccagagt cctgccctgg cccagcagca t 511

<210> 444
<211> 612
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(612)
<223> n = A,T,C or G

<400> 444
acaggaagaa ttctacagtt aatctatcac agtgttccag caaagcatat gttgaaaact 60
acagttttca atctaacatc taaattttaa aaagtagcat ttcagcaaca aacaagctca 120
gagaggctca tggcaaaagt gaaataacag aactattgct cagatgtctg caaagtcaag 180
ctgctgccct cagctccgcc cacttgaagg cttaggcaga cacgtaaggt ggcggtggct 240
ccttggcagc accattcaca gtggcatcat catacggagg tagcagcacc gtagtgtcat 300
tgctggtaac ataaaccagg acatcagagg agttcctacc attgatgtat cggtagcagt 360
tccaaacaca gctaatcaag taacccttaa aagtcaagat aatgctaata aacagaagaa 420
taataaggac caaacaggta ggattcactg acatgacatc atctctgtag ggaaaattag 480
gaggcagttg ccgtatgtat tcctgaatgg agtttggata aataagcaca gtgattgcaa 540
ccaacanctt cagggcaaag tcaaagatct ggtaacagaa gaatgggatg atccaggctg 600
cgcgttgctt gt 612

<210> 445
<211> 708
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(708)
<223> n = A,T,C or G

<400> 445
accatcctgt tccaacagag ccattgccta ttcctaaatt gaatctgact gggtgtgccc 60
ctcctcggaa cacaacagta gaccttaata gtggaaacat cgatgtgcct cccaacatga 120
caagctgggc cagctttcat aatggtgtgg ctgctggcct gaagatagct cctgcctccc 180
agatcgactc agcttggatt gtttacaata agcccaagca tgctgagttg gccaatgagt 240
atgctggctt tctcatggct ctgggtttga atgggcacct taccaagctg gcgactctca 300
atatccatga ctacttgacc aagggccatg aaatgacaag cattggactg ctacttggtg 360
tttctgctgc aaaactaggc accatggata tgtctattac tcggcttgtt agcattcgca 420
ttcctgctct cttaccccca acgtccacag agttggatgt tcctcacaat gtccaagtgg 480
ctgcagtggt tggcattggc cttgtatatc aagggacagc tcacagacat actgcagaag 540
tcctgttggc tgagatagga cggcctcctg gtcctgaaat ggaatactgc actgacagag 600
agtcatactc cttagctgct ggcttggccc tgggcatggt ctncttgggg catggcagca 660
atttgatagg tatgtntgat ctcaatgtgc ctgagcagct ctatcagt 708

<210> 446
<211> 612
<212> DNA
<213> Homo sapiens

<400> 446
acaagcaacg cgcagcctgg atcatcccat tcttctgtta ccagatcttt gactttgccc 60
tgaacatgtt ggttgcaatc actgtgctta tttatccaaa ctccattcag gaatacatac 120
ggcaactgcc tcctaatttt ccctacagag atgatgtcat gtcagtgaat cctacctgtt 180
tggtccttat tattcttctg tttattagca ttatcttgac ttttaagggt tacttgatta 240
gctgtgtttg gaactgctac cgatacatca atggtaggaa ctcctctgat gtcctggttt 300
atgttaccag caatgacact acggtgctgc taccccgta tgatgatgcc actgtgaatg 360
gtgctgccaa ggagccaccg ccaccttacg tgtctgccta agccttcaag tgggcggagc 420
tgagggcagc agcttgactt tgcagacatc tgagcaatag ttctgttatt tcacttttgc 480
catgagcctc tctgagcttg tttgttgctg aaatgctact ttttaaaatt tagatgttag 540
attgaaaact gtagttttca acatatgctt tgctggaaca ctgtgataga ttaactgtag 600
aattcttcct gt 612

<210> 447
<211> 642
<212> DNA
<213> Homo sapiens

<400> 447
actgaaagaa ttaaagtcag aagtcttccc aaaacaaaaa gaactgccca cagagaaaat 60
cctttctgat acttttcatt gctaaaataa aacaggcggg aaatgtggaa aagaaattca 120
acaaaatаat gtagcaccag aagaacaagt cctagatgat tcaagttcaa aaggtaagct 180
ccagcaatgt ggaagaggta aagaccaatg tagacaagct gacgaggaat atcttctttt 240
ttggttttct ggaagtagag ttcaggaaaa gcatgaagcc agtaagccag ctgtgatatg 300
tagaaaaact tcatttgaaa tgtcatcagg ttatggggat aagccctcca taagatagtt 360
gggtctgaga tgtagttttc agagatgaga atgaatgtgc cccaaacaca ggcaaaaagg 420
tagaacgcac taagctgacc agattcatta aacttgctgt gttttgtttt ggagaagtgc 480
attcgcctgt taattttatc caacatatac tcttgaatta cggcatgaat aattatcgcc 540
actagcatgt agaagaaaac agtagccaaa tctttgatgc catagtaata aagggacact 600
gattcagtag cttgttcttc tgttgctggg agggtgacat tg 642

<210> 448

<211> 394
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(394)
<223> n = A,T,C or G

<400> 448
accagaagac cttagaaaaa ggaggaaagg aggagaggca gataatttgg atgaattcct 60
caaagngttt gaaaatccag aggttcctag agaggaccag caacagcagc atcagcagcg 120
tgatgttatc gatgagccca ttattgaaga gccaagccgc ctccaggagt cagtgatgga 180
ggccagcaga acaaacatag atgagtcagc tatgcctcca ccaccacctc agggagttaa 240
gcgaaaagct ggacaaattg acccagagcc tgtgatgcct cctcagcagg tagagcagat 300
ggaaatacca cctgtagagc ttcccccaga agaacctcca aatatctgtc agctaatacc 360
agagttagaa cttctgccag aaaaagagaa ggag 394

<210> 449
<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 449
acaaaaaaca caaggaatac aacccaatag aaaatagtcc tgggaatgtg gtcagaagca 60
aaggcntgag tgtctttctc aaccgtgcaa aagccgtgtt cttcccggga aaccaggaaa 120
aggatccgct actcaaaaac caagaattta aaggagtttc ttaaatttcg accttgtttc 180
tgaagctcac ttttcagtgc cattgatgtg agatgtgctg gagtggctat taacctttt 240
ttcctaaaga ttattgttaa atagatattg tggtttgggg aagttgaatt ttttataggt 300
taaatgtcat tttagagatg gggagaggga ttatactgca ggcagcttca gccatgttgt 360
gaaactgata aaagcaactt agcaaggctt cttttcatta ttttttatgt ttcacttata 420
aagtcttagg taactagtag gatagaaaca ctgtgtcccg agagtaagga gagaagctac 480
tattgattag agcc 494

<210> 450
<211> 547
<212> DNA
<213> Homo sapiens

<400> 450
actttgggct ccagacttca ctgtccttag gcattgaaac catcacctgg tttgcattct 60
tcatgactga ggttaactta aaacaaaaat ggtaggaaag ctttcctatg cttcgggtaa 120
gagacaaatt tgcttttgta gaattggtgg ctgagaaagg cagacagggc ctgattaaag 180
aagacatttg tcaccactag ccaccaagtt aagttgtgga acccaaaggt gacggccatg 240
gaaacgtaga tcatcagctc tgctaagtag ttaggggaag aaacatattc aaaccagtct 300
ccaaatggga tcctgtggtt acagtgaatg gccactcctg ctttattttt cctgagattg 360
ccgagaataa catggcactt atactgatgg gcagatgacc agatgaacat catcatccca 420
agaatatgga accaccgtgc ttgcatcaat agatttttcc ctgttatgta ggcattcctg 480
ccatccattg gcacttggct cagcacagtt aggccaacaa ggacataata gacaagtcca 540
aaacagt 547

<210> 451
<211> 384
<212> DNA
<213> Homo sapiens

<220>

<221> misc_feature
<222> (1)...(384)
<223> n = A,T,C or G

<400> 451
actacttnnt ggttaaaang ccactggtag agtcatctga ntgtaaacaa tgtccctgca 60
ctgctggaaa aatccactgg ctcccaagaa aagaaaatgg tctgaagcct ctgttgtggc 120
tctcacaact catctttccc taagtcatca agctccacat cactgaggtc aatgtcatcc 180
tccacgggaa gctcgccatc cctgccgtcc caaggctctc tctcaacgat ggtagggaaa 240
gccccgcctc ctacaggtgc cgtggagcca cgcccaaaag agagctccct gagaaactcg 300
ttgatgcctt gctcactgaa ggagcctttt agcagagcaa atttcatctt gcgtgcattg 360
atggcggcca tggcggggta ccca 384

<210> 452
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(381)
<223> n = A,T,C or G

<400> 452
actctaaagt tgccactctc acaggggtca gtgataccca ctgaacctgg caggaacagt 60
cctgcagcca gaatctgcaa gcagcgcctg tatgcaacgt ttagggccaa aggctgtctg 120
gtggggttgt tcatcacagc ataatggcct agtaggtcaa ggatccaggg tgtgaggggc 180
tcaaagccag gaaaacgaat cctcaagtcc ttcagtagtc tgatgagaac tttaactgtg 240
gactgagaag cattttcctc gaaccagcgg gcatgtcgga tggctgctaa ngcactctgc 300
aatactttga tatccaaatg gagttctgga tccagttttc naagattggg tggcactgtt 360
gtaatganaa tcttcactgt a 381

<210> 453
<211> 455
<212> DNA
<213> Homo sapiens

<400> 453
actgtgctaa acagcctata gccaagtttt aaagagttac aggaacaact gctacacatt 60
caaagaacag gcattcactg cagcctcctg atttgacctg atgggaggga caggagaatg 120
agtcactctg ccaccacttt tcctgccttg gatttgtaga ggatttgttt tgctctaatt 180
tgtttttcct atatctgccc tactaaggta cacagtctgg gcactttgaa aatgttaaag 240
tttttaacgt ttgactgaca gaagcagcac ttaaaggctt catgaatcta ttttccaaaa 300
aaagtatgct ttcagtaaaa cattttacca ttttatctaa ctatgcactg acatttttgt 360
tcttcctgaa aaggggattt atgctaacac tgtatttta atgtaaaaat atacgtgtag 420
agatatttta acttcctgag tgacttatac ctcaa 455

<210> 454
<211> 383
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

<400> 454
acagagcanc tttacaagtt gtcacatttc tttataaatt tttttaaagc tacagtttaa 60
tacaaaatga attgcggttt tattacatta ataacctttc acctcagggt tttatgaaga 120
ggaaagggtt ttatgcaaaa gaaagtgcta caattcctaa tcattttaga cactttagga 180
gggggtgaag ttgtatgata aagcagatat tttaattatt tgttatcttt ttgtattgca 240

agaaatttct tgctagtgaa tcaagaaaac atccagattg acagtctaaa atggctactg 300
gtattttagt taattcaaaa atgaaacttt tcagtgattc actttactaa cattctattt 360
gagaaggctt attggtaaag ttt 383

<210> 455
<211> 383
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

<400> 455
actcctttan gacaaggaaa caggtatcag catgatggta gcagaaacct tatcaccaag 60
gtgcaggagc tgacttcttc caaagagttg tggttccggg cagcggtcat tgccgtgccc 120
attgctggag ggctgatttt agtgttgctt attatgttgg ccctgaggat gcttcgaagt 180
gaaaataaga ggctgcagga tcagcggcaa cagatgctct cccgtttgca ctacagcttt 240
cacggacacc attccaaaaa ggggcaggtt gcaaagttag acttggaatg catggtgccg 300
gtcagtgggc acgagaactg ctgtctgacc tgtgataaaa tgagacaagc agacctcagc 360
aacgataaga tcctctcgct tgt 383

<210> 456
<211> 543
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

<400> 456
acaaacattt tacaaaaaag aacattacca atatcagtgg cagtaagggc aagctgaaga 60
atangtagac tgagtttccg ggcaatgtct gtcctcaaag acatccaaac tgcgttcagg 120
cagctgaaac aggcttcttt cccagtgaca agcatatgtg gtcagtaata caaacgatgg 180
taaatgaggc tactacatag gcccagttaa caaactcctc ttctcctcgg gtaggccatg 240
atacaagtgg aactcatcaa ataatttaaa cccaaggcga taacaacact atttcccatc 300
taaactcatt taagccttca caatgtcgca atggattcag ttacttgcaa acgatcccgg 360
gttgtcatac agatacttgt tttttacaca taacgctgtg ccatcccttc cttcactgcc 420
ccagtcaggt ttcctgttgt tggaccgaaa ggggatacat tttagaaatg cttccctcaa 480
gacagaagtg agaaagaaag gagaccctga ggccaggatc tattaaacct ggtgtgtgcg 540
caa 543

<210> 457
<211> 544
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(544)
<223> n = A,T,C or G

<400> 457
actggtgcca atattgncat ggtgagctcc tctctaatgt cttccagggc accaatatct 60
gcccatgtca cattagggac agtgacaaag ccttcccttt tggcagaggg ttggactgag 120
gatagagcaa caatgaaatc attcagttca atgcacagtc cttgcatctg ctcctctgag 180
aggggatctt ggtctcttag caaccccagc agcctttgta attcatcctg tgtttcagaa 240
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gcctctcggc acagtgccat gagatcagca ccaacaaagc ctggagttag gtgtgctaag 420
tgacagaaat caaaagcttg aggaagcctc agttttctgc acaatgtttg aagtattctt 480
tccctggatg cttcatctgg gatacctagg catatttctc ggtcgaacct tcccgcacgt 540
ctca 544

<210> 458
<211> 382
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(382)
<223> n = A,T,C or G

<400> 458
acctntaggc tcaacggcag aancttcacc acaaaagcga aatgggcaca ccacagggag 60
aaaactggtt gtcctggatg tttgaaaagt tggtcgttgt catggtgtgt tacttcatcc 120
tatctatcat taactccatg gcacaaagtt atgccaaacg aatccagcag cggttgaact 180
cagaggagaa aactaaataa gtagagaaag ttttaaactg cagaaattgg agtggatggg 240
ttctgcctta aattgggagg actccaagcc gggaaggaaa attcccttt ccaacctgta 300
tcaattttta caacttttt cctgaaagca gtttagtcca tactttgcac tgacatactt 360
tttccttctg tgctaaggta ag 382

<210> 459
<211> 168
<212> DNA
<213> Homo sapiens

<400> 459
ctcgtactct agccaggcac gaaaccatga agtagcctga tccttcttag ccatcctggc 60
cgccttagcg gtagtaactt tgtgttatga atcacatgaa agcatggaat cttatgaact 120
taatcccttc attaacagga gaaatgcaaa taccttcata tcccctca 168

<210> 460
<211> 190
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(190)
<223> n = A,T,C or G

<400> 460
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catggatgga gcttcacacg atttcctcct gcggcagcgg cgaaggtcct ctactgctac 120
acctggcgtc accagtggcc cgtctgcctc aggaactcct ccgagtgagg gaggaggggg 180
ctcctttccc 190

<210> 461
<211> 495
<212> DNA
<213> Homo sapiens

<400> 461
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cccaagaatg gtttacacca agcagagagg acatgtcact gaatggggaa agggaacccc 180
cgtatccaca gtcactgtaa gcatccagta ggcaggaaga tggctttggg cagtggctgg 240
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tggtatatat gtggtcaaaa cgaattagtt cattaatggc ttccagcttg gctgatgacg 480
tccccactga cagag 495

<210> 462
<211> 493
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(493)
<223> n = A,T,C or G

<400> 462
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tctgccaagt gtgttttgga tacagagcac atcgtggctt ctggggtcac actcagctta 180
ggctgtgggt ccacagagca ctcatctggc tgggctatgg tggtggtggc tctactcaag 240
aagcaaagca gttaccagca cattcaaaca gtgtattgaa catcttttaa atatcaaagt 300
gagaaacaag aaggcaacat aataatgtta tcagaaagat gttaggaagt aaggacagct 360
gtgtaaagct tgaggctgaa aagtagcttg ccagcttcat ttctttggtt tcttgggtag 420
tgggcgccgg aacagcaaga tgtgaggttc tggttcatgg atcatataat ggacccatcc 480
ctgactctgc tga 493

<210> 463
<211> 3681
<212> DNA
<213> Homo sapiens

<400> 463
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caagagtaac atctaataaa actaaagttt tggaaaaagg aagatctaag atgattgcat 720
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gaagcctaca gacataaaat aacagtgtga agaattactt gttcacgaat tgcataaagc 3600
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tcgctctgtc actcaggctg g 3681

<210> 464
<211> 1424
<212> DNA
<213> Homo sapiens

<400> 464
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cacccgtggg taattaacct ggtcatcccc accctggaga gccatcctgc ccatgggtga 180
tcaaagaagg aacatctgca ggaacacctg atgaggctgc acccttggcg gaaagaacac 240
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<210> 465
<211> 674
<212> DNA
<213> Homo sapiens

<400> 465
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ggctagctgg ccctgtgggc atttattagt aaagttttaa tgacaaaagc tttgagtcaa 120
cacacccgtg ggtaattaac ctggtcatcc ccaccctgga gagccatcct gcccatgggt 180
gatcaaagaa ggaacatctg caggaacacc tgatgaggct gcacccttgg cggaaagaac 240
acctgacaca gctgaaagct tggtggaaaa aacacctgat gaggctgcac ccttggtgga 300
aagaacacct gacacggctg aaagcttggt ggaaaaaaca cctgatgagg ctgcatcctt 360
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acagtcagca gaagaaacac ctagggaaat tacgagtcct gcaaaagaaa catctgagaa 480
atttacgtgg ccagcaaaag gaagacctag gaagatcgca tgggagaaaa aagatgactc 540
agttaaggca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660
aaaaaaaaaa aaaa 674

<210> 466
<211> 1729
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (11)
<223> n=A,T,C or G
<221> unsure
<222> (1128)
<223> n=A,T,C or G

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aagaagacac acctagggaa attatgagtc ccgcaaaaga aacatctgag aaatttacgt 180
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ctggatgcgt ggcaagagta acatctaata aaactaaagt tttggaaaaa ggaagatcta 300
agatgattgc atgtcctaca aaagaatcat ctacaaaagc aagtgccaat gatcagaggt 360
tcccatcaga atccaaacaa gaggaagatg aagaatattc ttgtgattct cggagtctct 420
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aaatgcaaaa ctctgttcca aataaagcct ttgaattgaa gaatgaacaa acattgagag 600
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cctcctaaat gcaaaccatg gaaaaaaaga gaagtgcaat ggtcataagc tatgtgtctc 1620
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aattcaagat attccaagac gtgaggaaaa tgagaaaaaa aaaaaaaaa 1729

<210> 467
<211> 1337
<212> DNA
<213> Homo sapiens

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<210> 468
<211> 2307
<212> DNA
<213> Homo sapiens

<400> 468
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tacacatcaa aaagaaatag ataaaataaa tggaaaatta gaagggtctc ctgttaaaga 180
tggtcttctg aaggctaact gcggaatgaa agtttctatt ccaactaaag ccttagaatt 240
gatggacatg caaactttca aagcagagcc tcccgagaag ccatctgcct tcgagcctgc 300
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gagagcagat gagatactcc catcagaatc caaacaaaag gactatgaag aaagttcttg 420
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agagaccaac gtgaaacaca gtgtcaaatg aaggaagctg aacacatgta tcaaaacgaa 1740
caagataatg tgaacaaaca cactgaacag caggagtctc tagatcagaa attatttcaa 1800
ctacaaagca aaaatatgtg gcttcaacag caattagttc atgcacataa gaaagctgac 1860
aacaaaagca agataacaat tgatattcat tttcttgaga ggaaaatgca acatcatctc 1920
ctaaaagaga aaaatgagga gatatttaat tacaataacc atttaaaaaa ccgtatatat 1980
caatatgaaa aagagaaagc agaaacagaa aactcatgag agacaagcag taagaaactt 2040
cttttggaga aacaacagac cagatcttta ctcacaactc atgctaggag gccagtccta 2100
gcatcacctt atgttgaaaa tcttaccaat agtctgtgtc aacagaatac ttattttaga 2160
agaaaaattc atgatttctt cctgaagcct acagacataa aataacagtg tgaagaatta 2220
cttgttcacg aattgcataa agctgcacag gattcccatc taccctgatg atgcagcaga 2280
catcattcaa tccaaccaga atctcgc 2307

<210> 469
<211> 650
<212> PRT
<213> Homo sapiens

<220>
<221> unsure
<222> (310)
<223> Xaa = Any Amino Acid
<221> unsure
<222> (429)
<223> Xaa = Any Amino Acid
<221> unsure
<222> (522)
<223> Xaa = Any Amino Acid

<400> 469
Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys
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Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys
20 25 30
Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
35 40 45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
50 55 60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
65 70 75 80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
85 90 95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
100 105 110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
115 120 125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
130 135 140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
145 150 155 160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
165 170 175
Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His
180 185 190
Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asn
195 200 205
Lys Asp Gly Leu Leu Lys Ala Thr Cys Gly Met Lys Val Ser Ile Pro
210 215 220
Thr Lys Ala Leu Glu Leu Lys Asp Met Gln Thr Phe Lys Ala Glu Pro

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225                 230                 235                 240
Pro Gly Lys Pro Ser Ala Phe Glu Pro Ala Thr Glu Met Gln Lys Ser
                245                 250                 255
Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala
            260                 265                 270
Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser
        275                 280                 285
Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val
    290                 295                 300
Cys Leu Pro Lys Ala Xaa His Gln Lys Glu Ile Asp Lys Ile Asn Gly
305                 310                 315                 320
Lys Leu Glu Gly Ser Pro Val Lys Asp Gly Leu Leu Lys Ala Asn Cys
                325                 330                 335
Gly Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met
            340                 345                 350
Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
        355                 360                 365
Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
    370                 375                 380
Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys
385                 390                 395                 400
Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu
                405                 410                 415
Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Xaa His Gln Lys
            420                 425                 430
Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp
        435                 440                 445
Gly Phe Leu Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys
    450                 455                 460
Ala Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu
465                 470                 475                 480
Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro
                485                 490                 495
Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln
            500                 505                 510
Met Phe Pro Ser Glu Ser Lys Gln Lys Xaa Val Glu Glu Asn Ser Trp
        515                 520                 525
Asp Ser Glu Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val
    530                 535                 540
Pro Lys Ala Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu
545                 550                 555                 560
Glu Asp Ser Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys
                565                 570                 575
Glu Arg Ala Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly
            580                 585                 590
Lys Met Glu Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu
        595                 600                 605
Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys
    610                 615                 620
Trp Glu Gln Glu Leu Cys Ser Val Arg Phe Leu Thr Leu Met Lys Met
625                 630                 635                 640
Lys Ile Ile Ser Tyr Met Lys Ile Ala Cys
                645                 650
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<210> 470
<211> 228
<212> PRT
<213> Homo sapiens

<400> 470
Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys

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                  5                  10                  15
Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys
             20                  25                  30
Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
         35                  40                  45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
     50                  55                  60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
 65                  70                  75                  80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
                 85                  90                  95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
            100                 105                 110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
        115                 120                 125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
    130                 135                 140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
145                 150                 155                 160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
                165                 170                 175
Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His
            180                 185                 190
Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Gly Lys Asn Arg
        195                 200                 205
Phe Leu Phe Lys Asn Gln Leu Thr Glu Tyr Phe Ser Lys Leu Met Arg
    210                 215                 220
Arg Asp Ile Leu
225
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<210> 471
<211> 154
<212> PRT
<213> Homo sapiens

<220>
<221> unsure
<222> (148)
<223> Xaa = Any Amino Acid

<400> 471

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                  5                  10                  15
Trp Trp Lys Lys His Leu Met Arg Leu His Pro Trp Trp Lys Glu His
             20                  25                  30
Leu Thr Arg Leu Lys Ala Trp Trp Lys Lys His Leu Met Arg Leu His
         35                  40                  45
Pro Trp Trp Arg Glu His Leu Thr Lys Phe Asn Val Trp Arg Lys Arg
     50                  55                  60
His Leu Glu Ser Ser Asn Ser Gln Gln Lys Lys His Leu Gly Lys Leu
 65                  70                  75                  80
Arg Val Leu Gln Lys Lys His Leu Arg Asn Leu Arg Gly Gln Gln Lys
                 85                  90                  95
Glu Asp Leu Gly Arg Ser His Gly Arg Lys Lys Met Thr Gln Leu Arg
            100                 105                 110
Gln Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
        115                 120                 125
Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
    130                 135                 140
Lys Lys Lys Xaa Lys Lys Lys Lys Lys Lys
145                 150
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<210> 472
<211> 466
<212> PRT
<213> Homo sapiens

<220>
<221> unsure
<222> (329)
<223> Xaa = Any Amino Acid

<400> 472
Met Ser Pro Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys
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Gly Arg Pro Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys
20 25 30
Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
35 40 45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
50 55 60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
65 70 75 80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
85 90 95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
100 105 110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
115 120 125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
130 135 140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
145 150 155 160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
165 170 175
Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His
180 185 190
Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asn
195 200 205
Lys Asp Gly Leu Leu Lys Ala Thr Cys Gly Met Lys Val Ser Ile Pro
210 215 220
Thr Lys Ala Leu Glu Leu Lys Asp Met Gln Thr Phe Lys Ala Glu Pro
225 230 235 240
Pro Gly Lys Pro Ser Ala Phe Glu Pro Ala Thr Glu Met Gln Lys Ser
245 250 255
Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala
260 265 270
Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Asn
275 280 285
Ser Trp Asp Thr Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val
290 295 300
Cys Leu Pro Lys Ala Ala His Gln Lys Glu Ile Asp Lys Ile Asn Gly
305 310 315 320
Lys Leu Glu Gly Ser Pro Gly Lys Xaa Gly Leu Leu Lys Ala Asn Cys
325 330 335
Gly Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met
340 345 350
Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
355 360 365
Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
370 375 380
Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys

385 390 395 400
Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu
405 410 415
Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Ala His Gln Lys
420 425 430
Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Gly Lys Asn Arg Phe Leu
435 440 445
Phe Lys Asn His Leu Thr Lys Tyr Phe Ser Lys Leu Met Arg Lys Asp
450 455 460
Ile Leu
465

<210> 473
<211> 445
<212> PRT
<213> Homo sapiens

<400> 473
Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Gly Ser Pro Val Lys
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Asp Gly Leu Leu Lys Ala Asn Cys Gly Met Lys Val Ser Ile Pro Thr
20 25 30
Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro
35 40 45
Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val
50 55 60
Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp
65 70 75 80
Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser
85 90 95
Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys
100 105 110
Leu Pro Lys Ala Ala His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys
115 120 125
Leu Glu Glu Ser Pro Asp Asn Asp Gly Phe Leu Lys Ala Pro Cys Arg
130 135 140
Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln
145 150 155 160
Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala
165 170 175
Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn
180 185 190
Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro Ser Glu Ser Lys Gln
195 200 205
Lys Lys Val Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu Thr
210 215 220
Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala Thr His Gln Lys Glu
225 230 235 240
Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser Lys
245 250 255
Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln Lys
260 265 270
Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys
275 280 285
Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser
290 295 300
Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val
305 310 315 320
Arg Leu Thr Leu Asn Gln Glu Glu Glu Lys Arg Arg Asn Ala Asp Ile
325 330 335
Leu Asn Glu Lys Ile Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His

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            340                 345                 350
Arg Lys Glu Leu Glu Val Lys Gln Gln Leu Glu Gln Ala Leu Arg Ile
        355                 360                 365
Gln Asp Ile Glu Leu Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser
    370                 375                 380
His Thr His Glu Asn Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu
385                 390                 395                 400
Lys Lys Glu Ile Ala Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His
                405                 410                 415
Gln Tyr Gln Glu Lys Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu
            420                 425                 430
Lys Glu Lys Asn Ala Glu Leu Gln Met Thr Pro Arg Ala
        435                 440                 445
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<210> 474
<211> 3865
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (2448)...(2631)
<223> 184 bp insert of B726P splice form

<400> 474

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ctagctggcc ctgtgggcat ttattagtaa agttttaatg acaaaagctt tgagtcaaca     120
cacccgtggg taattaacct ggtcatcccc accctggaga gccatcctgc ccatgggtga     180
tcaaagaagg aacatctgca ggaacacctg atgaggctgc acccttggcg gaaagaacac     240
ctgacacagc tgaaagcttg gtggaaaaaa cacctgatga ggctgcaccc ttggtggaaa     300
gaacacctga cacggctgaa agcttggtgg aaaaaacacc tgatgaggct gcatccttgg     360
tggagggaac atctgacaaa attcaatgtt tggagaaagc gacatctgga aagttcgaac     420
agtcagcaga agaaacacct agggaaatta cgagtcctgc aaaagaaaca tctgagaaat     480
ttacgtggcc agcaaaagga agacctagga agatcgcatg ggagaaaaaa gaagacacac     540
ctagggaaat tatgagtccc gcaaaagaaa catctgagaa atttacgtgg gcagcaaaag     600
gaagacctag gaagatcgca tgggagaaaa aagaaacacc tgtaaagact ggatgcgtgg     660
caagagtaac atctaataaa actaaagttt tggaaaaagg aagatctaag atgattgcat     720
gtcctacaaa agaatcatct acaaaagcaa gtgccaatga tcagaggttc ccatcagaat     780
ccaaacaaga ggaagatgaa gaatattctt gtgattctcg gagtctcttt gagagttctg     840
caaagattca agtgtgtata cctgagtcta tatatcaaaa agtaatggag ataaatagag     900
aagtagaaga gcctcctaag aagccatctg ccttcaagcc tgccattgaa atgcaaaact     960
ctgttccaaa taaagccttt gaattgaaga atgaacaaac attgagagca gatccgatgt    1020
tcccaccaga atccaaacaa aaggactatg aagaaaattc ttgggattct gagagtctct    1080
gtgagactgt ttcacagaag gatgtgtgtt tacccaaggc tacacatcaa aaagaaatag    1140
ataaaataaa tggaaaatta gaagagtctc ctaataaaga tggtcttctg aaggctacct    1200
gcggaatgaa agtttctatt ccaactaaag ccttagaatt gaaggacatg caaactttca    1260
aagcagagcc tccggggaag ccatctgcct tcgagcctgc cactgaaatg caaaagtctg    1320
tcccaaataa agccttggaa ttgaaaaatg aacaaacatt gagagcagat gagatactcc    1380
catcagaatc caaacaaaag gactatgaag aaagttcttg ggattctgag agtctctgtg    1440
agactgtttc acagaaggat gtgtgtttac ccaaggctrc rcatcaaaaa gaaatagata    1500
aaataaatgg aaaattagaa gggtctcctg ttaaagatgg tcttctgaag gctaactgcg    1560
gaatgaaagt ttctattcca actaaagcct tagaattgat ggacatgcaa actttcaaag    1620
cagagcctcc cgagaagcca tctgccttcg agcctgccat tgaaatgcaa aagtctgttc    1680
caaataaagc cttggaattg aagaatgaac aaacattgag agcagatgag atactcccat    1740
cagaatccaa acaaaaggac tatgaagaaa gttcttggga ttctgagagt ctctgtgaga    1800
ctgtttcaca gaaggatgtg tgtttaccca aggctrcrca tcaaaaagaa atagataaaa    1860
taaatggaaa attagaagag tctcctgata atgatggttt tctgaaggct ccctgcagaa    1920
tgaaagtttc tattccaact aaagccttag aattgatgga catgcaaact ttcaaagcag    1980
agcctcccga gaagccatct gccttcgagc ctgccattga aatgcaaaag tctgttccaa    2040
ataaagcctt ggaattgaag aatgaacaaa cattgagagc agatcagatg ttcccttcag    2100
aatcaaaaca aaagaasgtt gaagaaaatt cttgggattc tgagagtctc cgtgagactg    2160
tttcacagaa ggatgtgtgt gtacccaagg ctacacatca aaaagaaatg gataaaataa    2220
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gtggaaaatt agaagattca actagcctat caaaaatctt ggatacagtt cattcttgtg 2280
aaagagcaag ggaacttcaa aaagatcact gtgaacaacg tacaggaaaa atggaacaaa 2340
tgaaaaagaa gttttgtgta ctgaaaaaga aactgtcaga agcaaaagaa ataaaatcac 2400
agttagagaa ccaaaaagtt aaatgggaac aagagctctg cagtgtgaga ttgactttaa 2460
accaagaaga agagaagaga agaaatgccg atatattaaa tgaaaaaatt agggaagaat 2520
taggaagaat cgaagagcag cataggaaag agttagaagt gaaacaacaa cttgaacagg 2580
ctctcagaat acaagatata gaattgaaga gtgtagaaag taatttgaat caggtttctc 2640
acactcatga aaatgaaaat tatctcttac atgaaaattg catgttgaaa aaggaaattg 2700
ccatgctaaa actggaaata gccacactga aacaccaata ccaggaaaag gaaaataaat 2760
actttgagga cattaagatt ttaaaagaaa agaatgctga acttcagatg accctaaaac 2820
tgaaagagga atcattaact aaaagggcat ctcaatatag tgggcagctt aaagttctga 2880
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cactttctga agctcaaagg aaatccaaaa gcctaaaaat taatctcaat tatgcmggag 3180
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agtgtcaaat gaaggaagct gaacacatgt atcaaaacga acaagataat gtgaacaaac 3300
acactgaaca gcaggagtct ctagatcaga aattatttca actacaaagc aaaaatatgt 3360
ggcttcaaca gcaattagtt catgcacata agaaagctga caacaaaagc aagataacaa 3420
ttgatattca ttttcttgag aggaaaatgc aacatcatct cctaaaagag aaaaatgagg 3480
agatatttaa ttacaataac catttaaaaa accgtatata tcaatatgaa aaagagaaag 3540
cagaaacaga aaactcatga gagacaagca gtaagaaact tcttttggag aaacaacaga 3600
ccagatcttt actcacaact catgctagga ggccagtcct agcatcacct tatgttgaaa 3660
atcttaccaa tagtctgtgt caacagaata cttattttag aagaaaaatt catgatttct 3720
tcctgaagcc tacagacata aaataacagt gtgaagaatt acttgttcac gaattgcata 3780
aagctgcaca ggattcccat ctaccctgat gatgcagcag acatcattca atccaaccag 3840
aatctcgctc tgtcactcag gctgg 3865

<210> 475
<211> 1002
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(1002)
<223> Xaa = Any Amino Acid

<400> 475
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Thr Gly Cys Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu
35 40 45
Lys Gly Arg Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr
50 55 60
Lys Ala Ser Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu
65 70 75 80
Glu Asp Glu Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser
85 90 95
Ala Lys Ile Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met
100 105 110
Glu Ile Asn Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe
115 120 125
Lys Pro Ala Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu
130 135 140
Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu
145 150 155 160
Ser Lys Gln Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu
165 170 175

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Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His
            180                 185                 190
Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asn
        195                 200                 205
Lys Asp Gly Leu Leu Lys Ala Thr Cys Gly Met Lys Val Ser Ile Pro
    210                 215                 220
Thr Lys Ala Leu Glu Leu Lys Asp Met Gln Thr Phe Lys Ala Glu Pro
225                 230                 235                 240
Pro Gly Lys Pro Ser Ala Phe Glu Pro Ala Thr Glu Met Gln Lys Ser
                245                 250                 255
Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala
            260                 265                 270
Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser
        275                 280                 285
Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val
    290                 295                 300
Cys Leu Pro Lys Ala Xaa His Gln Lys Glu Ile Asp Lys Ile Asn Gly
305                 310                 315                 320
Lys Leu Glu Gly Ser Pro Val Lys Asp Gly Leu Leu Lys Ala Asn Cys
                325                 330                 335
Gly Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met
            340                 345                 350
Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
        355                 360                 365
Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
    370                 375                 380
Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys
385                 390                 395                 400
Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu
                405                 410                 415
Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Xaa His Gln Lys
            420                 425                 430
Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp
        435                 440                 445
Gly Phe Leu Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys
    450                 455                 460
Ala Leu Glu Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu
465                 470                 475                 480
Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro
                485                 490                 495
Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln
            500                 505                 510
Met Phe Pro Ser Glu Ser Lys Gln Lys Xaa Val Glu Glu Asn Ser Trp
        515                 520                 525
Asp Ser Glu Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val
    530                 535                 540
Pro Lys Ala Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu
545                 550                 555                 560
Glu Asp Ser Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys
                565                 570                 575
Glu Arg Ala Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly
            580                 585                 590
Lys Met Glu Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu
        595                 600                 605
Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys
    610                 615                 620
Trp Glu Gln Glu Leu Cys Ser Val Arg Leu Thr Leu Asn Gln Glu Glu
625                 630                 635                 640
Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn Glu Lys Ile Arg Glu Glu
                645                 650                 655
Leu Gly Arg Ile Glu Glu Gln His Arg Lys Glu Leu Glu Val Lys Gln
            660                 665                 670
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Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val
        675                 680                 685
Glu Ser Asn Leu Asn Gln Val Ser His Thr His Glu Asn Glu Asn Tyr
    690                 695                 700
Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys
705                 710                 715                 720
Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys
                725                 730                 735
Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln
            740                 745                 750
Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln
        755                 760                 765
Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr
    770                 775                 780
Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile
785                 790                 795                 800
Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln
                805                 810                 815
Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly
            820                 825                 830
Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Ile
        835                 840                 845
Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala Gln Arg Lys
    850                 855                 860
Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp Ala Leu Arg
865                 870                 875                 880
Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln Arg Glu Thr
                885                 890                 895
Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn Glu Gln Asp
            900                 905                 910
Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp Gln Lys Leu
        915                 920                 925
Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln Leu Val His
    930                 935                 940
Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile Asp Ile His
945                 950                 955                 960
Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu Lys Asn Glu
                965                 970                 975
Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile Tyr Gln Tyr
            980                 985                 990
Glu Lys Glu Lys Ala Glu Thr Glu Asn Ser
        995                 1000
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<210> 476
<211> 356
<212> DNA
<213> Homo sapien

<400> 476

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aggtctgccg gaaatgttag gcaccccaac tcaagtccca ggccccaggc atctttcctg      60
ccctgccttg cttggcccat ccagtccagg cgcctggagc aagtgctcag ctacttctcc     120
tgcactttga aagacccctc ccactcctgg cctcacattt ctctgtgtga tcccccactt     180
ctgggctctg ccaccccaca gtgggaaagg ccaccctaga aagaagtccg ctggcaccca     240
taggaagggg cctcaggagc aggaagggcc aggaccagaa ccttgcccac ggcaactgcc     300
ttcctgcctc tccccttcct cctctgctct tgatctgtgt ttcaataaat taatgt         356
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<210> 477
<211> 1876
<212> DNA
<213> Homo sapien

<400> 477

atgacctgcg gatcaggatt tggtgggcgc gccttcagct gcatctcggc ctgcgggccg 60
cgccccggcc gctgctgcat caccgccgcc ccctaccgtg gcatctcctg ctaccgcggc 120
ctcaccgggg gcttcggcag ccacagcgtg tgcggaggct ttcgggccgg ctcctgcgga 180
cgcagcttcg gctaccgctc cgggggcgtg tgcgggccca gtcccccatg catcaccacc 240
gtgtcggtca acgagagcct cctcacgccc ctcaacctgg agatcgaccc caacgcgcag 300
tgcgtgaagc aggaggagaa ggagcagatc aagtccctca acagcaggtt cgcggccttc 360
atcgacaagg tgcgcttcct ggagcagcag aacaaactgc tggagacaaa gctgcagttc 420
taccagaacc gcgagtgttg ccagagcaac ctggagcccc tgtttgaggg ctacatcgag 480
actctgcggc gggaggccga gtgcgtggag gccgacagcg ggaggctggc ctcagagctt 540
aaccacgtgc aggaggtgct ggagggctac aagaagaagt atgaggagga ggtttctctg 600
agagcaacag ctgagaacga gtttgtggct ctgaagaagg atgtggactg cgcctacctc 660
cgcaagtcag acctggaggc caacgtggag gccctgatcc aggagatcga cttcctgagg 720
cggctgtatg aggaggagat ccgcattctc cagtcgcaca tctcagacac ctccgtggtt 780
gtcaagctgg acaacagccg ggacctgaac atggactgca tcattgccga gattaaggca 840
cagtatgacg acattgtcac ccgcagccgg gccgaggccg agtcctggta ccgcagcaag 900
tgtgaggaga tgaaggccac ggtgatcagg cacggggaga ccctgcgccg caccaaggag 960
gagatcaatg agctgaaccg catgatccaa aggctgacgg ccgaggtgga gaatgccaag 1020
tgccagaact ccaagctgga ggccgcggtg gctcagtctg agcagcaggg tgaggcagcc 1080
ctcagtgatg cccgctgcaa gctggccgag ctggagggcg ccctgcagaa ggccaagcag 1140
gacatggcct gcctgatcag ggagtaccag gaggtgatga actccaagct gggcctggac 1200
atcgagatcg ccacctacag gcgcctgctg gagggcgagg agcagaggct atgtgaaggc 1260
attggggctg tgaatgtctg tgtcagcagc tcccggggcg gggtcgtgtg cggggacctc 1320
tgcgtgtcag gctcccggcc agtgactggc agtgtctgca gcgctccgtg caacgggaac 1380
gtggcggtga gcaccggcct gtgtgcgccc tgcggccaat tgaacaccac ctgcggaggg 1440
ggttcctgcg gcgtgggctc ctgtggtatc agctccctgg gtgtggggtc ttgcggcagc 1500
agctgccgga aatgttaggc accccaactc aagtcccagg ccccaggcat ctttcctgcc 1560
ctgccttgct tggcccatcc agtccaggcg cctggagcaa gtgctcagct acttctcctg 1620
cactttgaaa gacccctccc actcctggcc tcacatttct ctgtgtgatc ccccacttct 1680
gggctctgcc accccacagt gggaaaggcc accctagaaa gaagtccgct ggcacccata 1740
ggaaggggcc tcaggagcag gaagggccag gaccagaacc ttgcccacgg caactgcctt 1800
cctgcctctc cccttcctcc tctgctcttg atctgtgttt caataaatta atgtagccaa 1860
aaaaaaaaaa aaaaaa 1876

<210> 478
<211> 505
<212> PRT
<213> Homo sapien

<400> 478
Met Thr Cys Gly Ser Gly Phe Gly Gly Arg Ala Phe Ser Cys Ile Ser
1 5 10 15
Ala Cys Gly Pro Arg Pro Gly Arg Cys Cys Ile Thr Ala Ala Pro Tyr
20 25 30
Arg Gly Ile Ser Cys Tyr Arg Gly Leu Thr Gly Gly Phe Gly Ser His
35 40 45
Ser Val Cys Gly Gly Phe Arg Ala Gly Ser Cys Gly Arg Ser Phe Gly
50 55 60
Tyr Arg Ser Gly Gly Val Cys Gly Pro Ser Pro Pro Cys Ile Thr Thr
65 70 75 80
Val Ser Val Asn Glu Ser Leu Leu Thr Pro Leu Asn Leu Glu Ile Asp
85 90 95
Pro Asn Ala Gln Cys Val Lys Gln Glu Glu Lys Glu Gln Ile Lys Ser
100 105 110
Leu Asn Ser Arg Phe Ala Ala Phe Ile Asp Lys Val Arg Phe Leu Glu
115 120 125
Gln Gln Asn Lys Leu Leu Glu Thr Lys Leu Gln Phe Tyr Gln Asn Arg
130 135 140
Glu Cys Cys Gln Ser Asn Leu Glu Pro Leu Phe Glu Gly Tyr Ile Glu
145 150 155 160
Thr Leu Arg Arg Glu Ala Glu Cys Val Glu Ala Asp Ser Gly Arg Leu
165 170 175
Ala Ser Glu Leu Asn His Val Gln Glu Val Leu Glu Gly Tyr Lys Lys

```
            180                 185                 190
Lys Tyr Glu Glu Glu Val Ser Leu Arg Ala Thr Ala Glu Asn Glu Phe
        195                 200                 205
Val Ala Leu Lys Lys Asp Val Asp Cys Ala Tyr Leu Arg Lys Ser Asp
    210                 215                 220
Leu Glu Ala Asn Val Glu Ala Leu Ile Gln Glu Ile Asp Phe Leu Arg
225                 230                 235                 240
Arg Leu Tyr Glu Glu Glu Ile Arg Ile Leu Gln Ser His Ile Ser Asp
                245                 250                 255
Thr Ser Val Val Val Lys Leu Asp Asn Ser Arg Asp Leu Asn Met Asp
            260                 265                 270
Cys Ile Ile Ala Glu Ile Lys Ala Gln Tyr Asp Asp Ile Val Thr Arg
        275                 280                 285
Ser Arg Ala Glu Ala Glu Ser Trp Tyr Arg Ser Lys Cys Glu Glu Met
    290                 295                 300
Lys Ala Thr Val Ile Arg His Gly Glu Thr Leu Arg Arg Thr Lys Glu
305                 310                 315                 320
Glu Ile Asn Glu Leu Asn Arg Met Ile Gln Arg Leu Thr Ala Glu Val
                325                 330                 335
Glu Asn Ala Lys Cys Gln Asn Ser Lys Leu Glu Ala Ala Val Ala Gln
            340                 345                 350
Ser Glu Gln Gln Gly Glu Ala Ala Leu Ser Asp Ala Arg Cys Lys Leu
        355                 360                 365
Ala Glu Leu Glu Gly Ala Leu Gln Lys Ala Lys Gln Asp Met Ala Cys
    370                 375                 380
Leu Ile Arg Glu Tyr Gln Glu Val Met Asn Ser Lys Leu Gly Leu Asp
385                 390                 395                 400
Ile Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly Glu Glu Gln Arg
                405                 410                 415
Leu Cys Glu Gly Ile Gly Ala Val Asn Val Cys Val Ser Ser Ser Arg
            420                 425                 430
Gly Gly Val Val Cys Gly Asp Leu Cys Val Ser Gly Ser Arg Pro Val
        435                 440                 445
Thr Gly Ser Val Cys Ser Ala Pro Cys Asn Gly Asn Val Ala Val Ser
    450                 455                 460
Thr Gly Leu Cys Ala Pro Cys Gly Gln Leu Asn Thr Thr Cys Gly Gly
465                 470                 475                 480
Gly Ser Cys Gly Val Gly Ser Cys Gly Ile Ser Ser Leu Gly Val Gly
                485                 490                 495
Ser Cys Gly Ser Ser Cys Arg Lys Cys
            500                 505
```

<210> 479
<211> 221
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(221)
<223> n = A,T,C or G

<400> 479
ggtccattcc tttcctcgcg tngggtttc tctgtgtcag cgagcctcgg tacactgatt 60
tccgatcaaa agaatcatca tctttacctt gacttttcag ggaattactg aactttcttc 120
tcagaagata gggcacagcc attgccttgg cctcacttga agggtctgca tttgggtcct 180
ctggtctctt gccaagtttc ccagccactc gagggagaaa t 221

<210> 480
<211> 36
<212> DNA

<213> Artificial Sequence

<220>
<223> PCR primer

<400> 480
cggcgaattc accatgggaa caagagctct gcagtg 36

<210> 481
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 481
cggcaagctt ttaatggtga tggtgatgat gtataacttc tgtttctgct ttctcttttt 60
ca 62

<210> 482
<211> 972
<212> DNA
<213> Homo sapiens

<400> 482
atgggaacaa gagctctgca gtgtgaggtt tctcacactc atgaaaatga aaattatctc 60
ttacatgaaa attgcatgtt gaaaaaggaa attgccatgc taaaactgga aatagccaca 120
ctgaaacacc aataccagga aaaggaaaat aaatactttg aggacattaa gattttaaaa 180
gaaaagaatg ctgaacttca gatgacccta aaactgaaag aggaatcatt aactaaaagg 240
gcatctcaat atagtgggca gcttaaagtt ctgatagctg agaacacaat gctcacttct 300
aaattgaagg aaaaacaaga caaagaaata ctagaggcag aaattgaatc acaccatcct 360
agactggctt ctgctgtaca agaccatgat caaattgtga catcaagaaa aagtcaagaa 420
cctgctttcc acattgcagg agatgcttgt ttgcaaagaa aaatgaatgt tgatgtgagt 480
agtacgatat ataacaatga ggtgctccat caaccacttt ctgaagctca aaggaaatcc 540
aaaagcctaa aaattaatct caattatgcc ggagatgctc taagagaaaa tacattggtt 600
tcagaacatg cacaaagaga ccaacgtgaa acacagtgtc aaatgaagga agctgaacac 660
atgtatcaaa acgaacaaga taatgtgaac aaacacactg aacagcagga gtctctagat 720
cagaaattat ttcaactaca aagcaaaaat atgtggcttc aacagcaatt agttcatgca 780
cataagaaag ctgacaacaa aagcaagata acaattgata ttcattttct tgagaggaaa 840
atgcaacatc atctcctaaa agagaaaaat gaggagatat ttaattacaa taaccattta 900
aaaaaccgta tatatcaata tgaaaaagag aaagcagaaa cagaagttat acatcatcac 960
catcaccatt aa 972

<210> 483
<211> 323
<212> PRT
<213> Homo sapiens

<400> 483
Met Gly Thr Arg Ala Leu Gln Cys Glu Val Ser His Thr His Glu Asn
1 5 10 15
Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala
20 25 30
Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
35 40 45
Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
50 55 60
Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg
65 70 75 80
Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr

```
                85                  90                  95
Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu
            100                 105                 110
Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp
        115                 120                 125
His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His
    130                 135                 140
Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser
145                 150                 155                 160
Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala
                165                 170                 175
Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp
            180                 185                 190
Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln
        195                 200                 205
Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn
    210                 215                 220
Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp
225                 230                 235                 240
Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln
                245                 250                 255
Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile
            260                 265                 270
Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu
        275                 280                 285
Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile
    290                 295                 300
Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Val Ile His His His
305                 310                 315                 320
His His His
```

<210> 484
<211> 1518
<212> DNA
<213> Homo sapiens

<400> 484

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atgacctgcg gatcaggatt tggtgggcgc gccttccgct gcatctcggc ctgcgggccg 60
cggcccggcc gctgctgcat caccgccgcc ccctaccgtg gcatctcctg ctaccgcggc 120
ctcaccgggg gcttcggcag ccacagcgtg tgcggaggct ttcgggccgg ctcctgcgga 180
cgcagcttcg gctaccgctc cgggggcgtg tgcgggccca gtcccccatg catcaccacc 240
gtgtcggtca acgagagcct cctcacgccc ctcaacctgg agatcgaccc caacgcgcag 300
tgcgtgaagc aggaggagaa ggagcagatc aagtccctca acagcaggtt cgcggccttc 360
atcgacaagg tgcgcttcct ggagcagcag aacaaactgc tggagacaaa gctgcagttc 420
taccagaacc gcgagtgttg ccagagcaac ctggagcccc tgtttgaggg ctacatcgag 480
actctgcggc gggaggccga gtgcgtggag gccgacagcg ggaggctggc ctcagagctt 540
aaccacgtgc aggaggtgct ggagggctac aagaagaagt atgaggagga ggtttctctg 600
agagcaacag ctgagaacga gtttgtggct ctgaagaagg atgtggactg cgcctacctc 660
cgcaagtcag acctggaggc caacgtggag gccctgatcc aggagatcga cttcctgagg 720
cggctgtatg aggaggagat ccgcattctc cagtcgcaca tctcagacac ctccgtggtt 780
gtcaagctgg acaacagccg ggacctgaac atggactgca tcattgccga gattaaggca 840
cagtatgacg acattgtcac ccgcagccgg gccgaggccg agtcctggta ccgcagcaag 900
tgtgaggaga tgaaggccac ggtgatcagg cacggggaga ccctgcgccg caccaaggag 960
gagatcaatg agctgaaccg catgatccaa aggctgacgg ccgaggtgga gaatgccaag 1020
tgccagaact ccaagctgga ggccgcggtg gcccagtctg agcagcaggg tgaggcagcc 1080
ctcagtgatg cccgctgcaa gctggccgag ctggagggcg ccctgcagaa ggccaagcag 1140
gacatggcct gcctgatcag ggagtaccag gaggtgatga actccaagct gggcctggac 1200
atcgagatcg ccacctacag gcgcctgctg gagggcgagg agcagaggct atgtgaaggc 1260
attggggctg tgaatgtctg tgtcagcagc tcccggggcg gggtcgtgtg cggggacctc 1320
tgcgtgtcag gctcccggcc agtgactggc agtgtctgca gcgctccgtg caacgggaac 1380
gtggcggtga gcaccggcct gtgtgcgccc tgcggccaat tgaacaccac ctgcggaggg 1440
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ggttcctgcg gcgtgggctc ctgtggtatc agctccctgg gtgtggggtc ttgcggcagc 1500
agctgccgga aatgttag 1518

<210> 485
<211> 505
<212> PRT
<213> Homo sapiens

<400> 485
Met Thr Cys Gly Ser Gly Phe Gly Gly Arg Ala Phe Arg Cys Ile Ser
1 5 10 15
Ala Cys Gly Pro Arg Pro Gly Arg Cys Cys Ile Thr Ala Ala Pro Tyr
20 25 30
Arg Gly Ile Ser Cys Tyr Arg Gly Leu Thr Gly Gly Phe Gly Ser His
35 40 45
Ser Val Cys Gly Gly Phe Arg Ala Gly Ser Cys Gly Arg Ser Phe Gly
50 55 60
Tyr Arg Ser Gly Gly Val Cys Gly Pro Ser Pro Pro Cys Ile Thr Thr
65 70 75 80
Val Ser Val Asn Glu Ser Leu Leu Thr Pro Leu Asn Leu Glu Ile Asp
85 90 95
Pro Asn Ala Gln Cys Val Lys Gln Glu Glu Lys Glu Gln Ile Lys Ser
100 105 110
Leu Asn Ser Arg Phe Ala Ala Phe Ile Asp Lys Val Arg Phe Leu Glu
115 120 125
Gln Gln Asn Lys Leu Leu Glu Thr Lys Leu Gln Phe Tyr Gln Asn Arg
130 135 140
Glu Cys Cys Gln Ser Asn Leu Glu Pro Leu Phe Glu Gly Tyr Ile Glu
145 150 155 160
Thr Leu Arg Arg Glu Ala Glu Cys Val Glu Ala Asp Ser Gly Arg Leu
165 170 175
Ala Ser Glu Leu Asn His Val Gln Glu Val Leu Glu Gly Tyr Lys Lys
180 185 190
Lys Tyr Glu Glu Glu Val Ser Leu Arg Ala Thr Ala Glu Asn Glu Phe
195 200 205
Val Ala Leu Lys Lys Asp Val Asp Cys Ala Tyr Leu Arg Lys Ser Asp
210 215 220
Leu Glu Ala Asn Val Glu Ala Leu Ile Gln Glu Ile Asp Phe Leu Arg
225 230 235 240
Arg Leu Tyr Glu Glu Glu Ile Arg Ile Leu Gln Ser His Ile Ser Asp
245 250 255
Thr Ser Val Val Val Lys Leu Asp Asn Ser Arg Asp Leu Asn Met Asp
260 265 270
Cys Ile Ile Ala Glu Ile Lys Ala Gln Tyr Asp Asp Ile Val Thr Arg
275 280 285
Ser Arg Ala Glu Ala Glu Ser Trp Tyr Arg Ser Lys Cys Glu Glu Met
290 295 300
Lys Ala Thr Val Ile Arg His Gly Glu Thr Leu Arg Arg Thr Lys Glu
305 310 315 320
Glu Ile Asn Glu Leu Asn Arg Met Ile Gln Arg Leu Thr Ala Glu Val
325 330 335
Glu Asn Ala Lys Cys Gln Asn Ser Lys Leu Glu Ala Ala Val Ala Gln
340 345 350
Ser Glu Gln Gln Gly Glu Ala Ala Leu Ser Asp Ala Arg Cys Lys Leu
355 360 365
Ala Glu Leu Glu Gly Ala Leu Gln Lys Ala Lys Gln Asp Met Ala Cys
370 375 380
Leu Ile Arg Glu Tyr Gln Glu Val Met Asn Ser Lys Leu Gly Leu Asp
385 390 395 400
Ile Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly Glu Glu Gln Arg
405 410 415
Leu Cys Glu Gly Ile Gly Ala Val Asn Val Cys Val Ser Ser Ser Arg

```
            420                 425                 430
Gly Gly Val Val Cys Gly Asp Leu Cys Val Ser Gly Ser Arg Pro Val
        435                 440                 445
Thr Gly Ser Val Cys Ser Ala Pro Cys Asn Gly Asn Val Ala Val Ser
    450                 455                 460
Thr Gly Leu Cys Ala Pro Cys Gly Gln Leu Asn Thr Thr Cys Gly Gly
465                 470                 475                 480
Gly Ser Cys Gly Val Gly Ser Cys Gly Ile Ser Ser Leu Gly Val Gly
                485                 490                 495
Ser Cys Gly Ser Ser Cys Arg Lys Cys
            500                 505
```

<210> 486
<211> 827
<212> DNA
<213> Homo sapiens

<400> 486
gcattctcca gtcgcacatc tcagacacct ccgtggttgt caagctggac aacagccggg 60
acctgaacat ggactgcatc attgccgaga ttaaggcaca gtatgacgac attgtcaccc 120
gcagccgggc cgaggccgag tcctggtacc gcagcaagtg tgaggagatg aaggccacgg 180
tgatcaggca cggggagacc ctgcgccgca ccaaggagga gatcaatgag ctgaaccgca 240
tgatccaaag gctgacggcc gaggtggaga atgccaagtg ccagaactcc aagctggagg 300
ccgcggtggc ccagtctgag cagcagggtg aggcagccct cagtgatgcc cgctgcaagc 360
tggccgagct ggagggcgcc ctgcagaagg ccaagcagga catggcctgc ctgatcaggg 420
agtaccagga ggtgatgaac tccaagctgg gcctggacat cgagatcgcc acctacaggc 480
gcctgctgga gggcgaggag cagaggctat gtgaaggcat tggggctgtg aatgtctgtg 540
tcagcagctc ccggggcggg gtcgtgtgcg gggacctctg cgtgtcaggc tcccggccag 600
tgactggcag tgtctgcagc gctccgtgca acgggaacgt ggcggtgagc accggcctgt 660
gtgcgccctg cggccaattg aacaccacct gcggaggggg ttcctgcggc gtgggctcct 720
gtggtatcag ctccctgggt gtggggtctt gcggcagcag ctgccggaaa tgttaggcac 780
cccaactcaa gtcccaggcc ccaggcatct ttcctgccct gccttgc 827

<210> 487
<211> 235
<212> PRT
<213> Homo sapiens

<400> 487
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Met Asp Cys Ile Ile Ala Glu Ile Lys Ala Gln Tyr Asp Asp Ile Val
                5                  10                  15
Thr Arg Ser Arg Ala Glu Ala Glu Ser Trp Tyr Arg Ser Lys Cys Glu
            20                  25                  30
Glu Met Lys Ala Thr Val Ile Arg His Gly Glu Thr Leu Arg Arg Thr
        35                  40                  45
Lys Glu Glu Ile Asn Glu Leu Asn Arg Met Ile Gln Arg Leu Thr Ala
    50                  55                  60
Glu Val Glu Asn Ala Lys Cys Gln Asn Ser Lys Leu Glu Ala Ala Val
65                  70                  75                  80
Ala Gln Ser Glu Gln Gln Gly Glu Ala Ala Leu Ser Asp Ala Arg Cys
                85                  90                  95
Lys Leu Ala Glu Leu Glu Gly Ala Leu Gln Lys Ala Lys Gln Asp Met
            100                 105                 110
Ala Cys Leu Ile Arg Glu Tyr Gln Glu Val Met Asn Ser Lys Leu Gly
        115                 120                 125
Leu Asp Ile Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly Glu Glu
    130                 135                 140
Gln Arg Leu Cys Glu Gly Ile Gly Ala Val Asn Val Cys Val Ser Ser
145                 150                 155                 160
Ser Arg Gly Gly Val Val Cys Gly Asp Leu Cys Val Ser Gly Ser Arg
                165                 170                 175
```

```
Pro Val Thr Gly Ser Val Cys Ser Ala Pro Cys Asn Gly Asn Val Ala
            180                 185                 190
Val Ser Thr Gly Leu Cys Ala Pro Cys Gly Gln Leu Asn Thr Thr Cys
        195                 200                 205
Gly Gly Gly Ser Cys Gly Val Gly Ser Cys Gly Ile Ser Ser Leu Gly
    210                 215                 220
Val Gly Ser Cys Gly Ser Ser Cys Arg Lys Cys
225                 230                 235
```

<210> 488
<211> 9
<212> PRT
<213> Homo sapiens

<400> 488
Ser Leu Thr Lys Arg Ala Ser Gln Tyr
5

<210> 489
<211> 27

<212> DNA
<213> Homo sapiens

<400> 489
tcattaacta aaagggcatc tcaatat 27

<210> 490
<211> 3288
<212> DNA
<213> Homo sapiens

<400> 490
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ggctgccccc tattggagaa tgtgatttcc aagacaatca atccacaagt gtctaagact 120
gaatacaaag aacttcttca agagttcata gacgacaatg ccactacaaa tgccatagat 180
gaattgaagg aatgttttct taaccaaacg gatgaaactc tgagcaatgt tgaggtgttt 240
atgcaattaa tatatgacag cagtctttgt gatttattta tgagtcccgc aaaagaaaca 300
tctgagaaat ttacgtgggc agcaaaagga agacctagga agatcgcatg ggagaaaaaa 360
gaaacacctg taaagactgg atgcgtggca agagtaacat ctaataaaac taaagttttg 420
gaaaaaggaa gatctaagat gattgcatgt cctacaaaag aatcatctac aaaagcaagt 480
gccaatgatc agaggttccc atcagaatcc aaacaagagg aagatgaaga atattcttgt 540
gattctcgga gtctctttga gagttctgca aagattcaag tgtgtatacc tgagtctata 600
tatcaaaaag taatggagat aaatagagaa gtagaagagc ctcctaagaa gccatctgcc 660
ttcaagcctg ccattgaaat gcaaaactct gttccaaata aagcctttga attgaagaat 720
gaacaaacat tgagagcaga tccgatgttc ccaccagaat ccaaacaaaa ggactatgaa 780
gaaaattctt gggattctga gagtctctgt gagactgttt cacagaagga tgtgtgttta 840
cccaaggcta cacatcaaaa agaaatagat aaaataaatg gaaaattaga agagtctcct 900
aataaagatg gtcttctgaa ggctacctgc ggaatgaaag tttctattcc aactaaagcc 960
ttagaattga aggacatgca aactttcaaa gcagagcctc cggggaagcc atctgccttc 1020
gagcctgcca ctgaaatgca aaagtctgtc ccaaataaag ccttggaatt gaaaaatgaa 1080
caaacattga gagcagatga gatactccca tcagaatcca aacaaaagga ctatgaagaa 1140
agttcttggg attctgagag tctctgtgag actgtttcac agaaggatgt gtgtttaccc 1200
aaggctrcrc atcaaaaaga aatagataaa ataaatggaa aattagaagg gtctcctgtt 1260
aaagatggtc ttctgaaggc taactgcgga atgaaagttt ctattccaac taaagcctta 1320
gaattgatgg acatgcaaac tttcaaagca gagcctcccg agaagccatc tgccttcgag 1380
cctgccattg aaatgcaaaa gtctgttcca aataaagcct tggaattgaa gaatgaacaa 1440
acattgagag cagatgagat actcccatca gaatccaaac aaaaggacta tgaagaaagt 1500
tcttgggatt ctgagagtct ctgtgagact gtttcacaga aggatgtgtg tttacccaag 1560
gctrcrcatc aaaaagaaat agataaaata aatggaaaat tagaagagtc tcctgataat 1620
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gatggttttc tgaaggctcc ctgcagaatg aaagtttcta ttccaactaa agccttagaa 1680
ttgatggaca tgcaaacttt caaagcagag cctcccgaga agccatctgc cttcgagcct 1740
gccattgaaa tgcaaaagtc tgttccaaat aaagccttgg aattgaagaa tgaacaaaca 1800
ttgagagcag atcagatgtt cccttcagaa tcaaaacaaa agaasgttga agaaaattct 1860
tgggattctg agagtctccg tgagactgtt tcacagaagg atgtgtgtgt acccaaggct 1920
acacatcaaa aagaaatgga taaaataagt ggaaaattag aagattcaac tagcctatca 1980
aaaatcttgg atacagttca ttcttgtgaa agagcaaggg aacttcaaaa agatcactgt 2040
gaacaacgta caggaaaaat ggaacaaatg aaaaagaagt tttgtgtact gaaaaagaaa 2100
ctgtcagaag caaaagaaat aaaatcacag ttagagaacc aaaaagttaa atgggaacaa 2160
gagctctgca gtgtgagatt gactttaaac caagaagaag agaagagaag aaatgccgat 2220
atattaaatg aaaaaattag ggaagaatta ggaagaatcg aagagcagca taggaaagag 2280
ttagaagtga aacaacaact tgaacaggct ctcagaatac aagatataga attgaagagt 2340
gtagaaagta atttgaatca ggtttctcac actcatgaaa atgaaaatta tctcttacat 2400
gaaaattgca tgttgaaaaa ggaaattgcc atgctaaaac tggaaatagc cacactgaaa 2460
caccaatacc aggaaaagga aaataaatac tttgaggaca ttaagatttt aaaagaaaag 2520
aatgctgaac ttcagatgac cctaaaactg aaagaggaat cattaactaa aagggcatct 2580
caatatagtg ggcagcttaa agttctgata gctgagaaca caatgctcac ttctaaattg 2640
aaggaaaaac aagacaaaga aatactagag gcagaaattg aatcacacca tcctagactg 2700
gcttctgctg tacaagacca tgatcaaatt gtgacatcaa gaaaaagtca agaacctgct 2760
ttccacattg caggagatgc ttgtttgcaa agaaaaatga atgttgatgt gagtagtacg 2820
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ctaaaaatta atctcaatta tgcmggagat gctctaagag aaaatacatt ggtttcagaa 2940
catgcacaaa gagaccaacg tgaaacacag tgtcaaatga aggaagctga acacatgtat 3000
caaaacgaac aagataatgt gaacaaacac actgaacagc aggagtctct agatcagaaa 3060
ttatttcaac tacaaagcaa aaatatgtgg cttcaacagc aattagttca tgcacataag 3120
aaagctgaca acaaaagcaa gataacaatt gatattcatt ttcttgagag gaaaatgcaa 3180
catcatctcc taaaagagaa aaatgaggag atatttaatt acaataacca tttaaaaaac 3240
cgtatatatc aatatgaaaa agagaaagca gaaacagaaa actcatga 3288

<210> 491
<211> 2232
<212> DNA
<213> Homo sapiens

<400> 491
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ggctgcccct tattggagaa tgtgatttcc aagacaatca atccacaagt gtctaagact 120
gaatacaaag aacttcttca agagttcata gacgacaatg ccactacaaa tgccatagat 180
gaattgaagg aatgttttct taaccaaacg gatgaaactc tgagcaatgt tgaggtgttt 240
atgcaattaa tatatgacag cagtctttgt gatttattta tgagtcccgc aaaagaaaca 300
tctgagaaat ttacgtgggc agcaaaagga agacctagga agatcgcatg ggagaaaaaa 360
gaaacacctg taaagactgg atgcgtggca agagtaacat ctaataaaac taaagttttg 420
gaaaaaggaa gatctaagat gattgcatgt cctacaaaag aatcatctac aaaagcaagt 480
gccaatgatc agaggttccc atcagaatcc aaacaagagg aagatgaaga atattcttgt 540
gattctcgga gtctctttga gagttctgca aagattcaag tgtgtatacc tgagtctata 600
tatcaaaaag taatggagat aaatagagaa gtagaagagc ctcctaagaa gccatctgcc 660
ttcaagcctg ccattgaaat gcaaaactct gttccaaata aagcctttga attgaagaat 720
gaacaaacat tgagagcaga tccgatgttc ccaccagaat ccaaacaaaa ggactatgaa 780
gaaaattctt gggattctga gagtctctgt gagactgttt cacagaagga tgtgtgttta 840
cccaaggcta cacatcaaaa agaaatagat aaaataaatg gaaaattaga agagtctcct 900
aataaagatg gtcttctgaa ggctacctgc ggaatgaaag tttctattcc aactaaagcc 960
ttagaattga aggacatgca aactttcaaa gcagagcctc cggggaagcc atctgccttc 1020
gagcctgcca ctgaaatgca aaagtctgtc ccaaataaag ccttggaatt gaaaaatgaa 1080
caaacattga gagcagatga gatactccca tcagaatcca aacaaaagga ctatgaagaa 1140
agttcttggg attctgagag tctctgtgag actgtttcac agaaggatgt gtgtttaccc 1200
aaggctrcrc atcaaaaaga aatagataaa ataaatggaa aattagaagg gtctcctgtt 1260
aaagatggtc ttctgaaggc taactgcgga atgaaagttt ctattccaac taaagcctta 1320
gaattgatgg acatgcaaac tttcaaagca gagcctcccg agaagccatc tgccttcgag 1380
cctgccattg aaatgcaaaa gtctgttcca aataaagcct tggaattgaa gaatgaacaa 1440
acattgagag cagatgagat actcccatca gaatccaaac aaaaggacta tgaagaaagt 1500
tcttgggatt ctgagagtct ctgtgagact gtttcacaga aggatgtgtg tttacccaag 1560
gctrcrcatc aaaaagaaat agataaaata aatggaaaat tagaagagtc tcctgataat 1620

gatggttttc tgaaggctcc ctgcagaatg aaagtttcta ttccaactaa agccttagaa 1680
ttgatggaca tgcaaacttt caaagcagag cctcccgaga agccatctgc cttcgagcct 1740
gccattgaaa tgcaaaagtc tgttccaaat aaagccttgg aattgaagaa tgaacaaaca 1800
ttgagagcag atcagatgtt cccttcagaa tcaaaacaaa agaasgttga agaaaattct 1860
tgggattctg agagtctccg tgagactgtt tcacagaagg atgtgtgtgt acccaaggct 1920
acacatcaaa aagaaatgga taaaataagt ggaaaattag aagattcaac tagcctatca 1980
aaaatcttgg atacagttca ttcttgtgaa agagcaaggg aacttcaaaa agatcactgt 2040
gaacaacgta caggaaaaat ggaacaaatg aaaaagaagt tttgtgtact gaaaaagaaa 2100
ctgtcagaag caaaagaaat aaaatcacag ttagagaacc aaaaagttaa atgggaacaa 2160
gagctctgca gtgtgaggtt tctcacactc atgaaaatga aaattatctc ttacatgaaa 2220
attgcatgtt ga 2232

<210> 492
<211> 1233
<212> DNA
<213> Homo sapiens

<400> 492
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ggctgcccct tattggagaa tgtgatttcc aagacaatca atccacaagt gtctaagact 120
gaatacaaag aacttcttca agagttcata gacgacaatg ccactacaaa tgccatagat 180
gaattgaagg aatgttttct taaccaaacg gatgaaactc tgagcaatgt tgaggtgttt 240
atgcaattaa tatatgacag cagtctttgt gatttattta tgggaacaag agctctgcag 300
tgtgaggttt ctcacactca tgaaaatgaa aattatctct tacatgaaaa ttgcatgttg 360
aaaaaggaaa ttgccatgct aaaactggaa atagccacac tgaaacacca ataccaggaa 420
aaggaaaata aatactttga ggacattaag attttaaaag aaaagaatgc tgaacttcag 480
atgaccctaa aactgaaaga ggaatcatta actaaaaggg catctcaata tagtgggcag 540
cttaaagttc tgatagctga gaacacaatg ctcacttcta aattgaagga aaaacaagac 600
aaagaaatac tagaggcaga aattgaatca caccatccta gactggcttc tgctgtacaa 660
gaccatgatc aaattgtgac atcaagaaaa agtcaagaac ctgctttcca cattgcagga 720
gatgcttgtt tgcaaagaaa aatgaatgtt gatgtgagta gtacgatata taacaatgag 780
gtgctccatc aaccactttc tgaagctcaa aggaaatcca aaagcctaaa aattaatctc 840
aattatgccg gagatgctct aagagaaaat acattggttt cagaacatgc acaaagagac 900
caacgtgaaa cacagtgtca aatgaaggaa gctgaacaca tgtatcaaaa cgaacaagat 960
aatgtgaaca aacacactga acagcaggag tctctagatc agaaattatt tcaactacaa 1020
agcaaaaata tgtggcttca acagcaatta gttcatgcac ataagaaagc tgacaacaaa 1080
agcaagataa caattgatat tcattttctt gagaggaaaa tgcaacatca tctcctaaaa 1140
gagaaaaatg aggagatatt taattacaat aaccatttaa aaaaccgtat atatcaatat 1200
gaaaaagaga aagcagaaac agaagttata taa 1233

<210> 493
<211> 1095
<212> PRT
<213> Homo sapiens

<220>
<221> variant
<222> (1)...(1095)
<223> Xaa = Any amino acid

<400> 493
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Tyr Ala Gly Ser Gly Cys Pro Leu Leu Glu Asn Val Ile Ser Lys Thr
20 25 30
Ile Asn Pro Gln Val Ser Lys Thr Glu Tyr Lys Glu Leu Leu Gln Glu
35 40 45
Phe Ile Asp Asp Asn Ala Thr Thr Asn Ala Ile Asp Glu Leu Lys Glu
50 55 60
Cys Phe Leu Asn Gln Thr Asp Glu Thr Leu Ser Asn Val Glu Val Phe
65 70 75 80
Met Gln Leu Ile Tyr Asp Ser Ser Leu Cys Asp Leu Phe Met Ser Pro

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                    85                  90                  95
Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys Gly Arg Pro
            100                 105                 110
Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys Thr Gly Cys
        115                 120                 125
Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu Lys Gly Arg
    130                 135                 140
Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr Lys Ala Ser
145                 150                 155                 160
Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu Glu Asp Glu
                165                 170                 175
Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser Ala Lys Ile
            180                 185                 190
Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met Glu Ile Asn
        195                 200                 205
Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe Lys Pro Ala
    210                 215                 220
Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu Leu Lys Asn
225                 230                 235                 240
Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu Ser Lys Gln
                245                 250                 255
Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr
            260                 265                 270
Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His Gln Lys Glu
        275                 280                 285
Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asn Lys Asp Gly
    290                 295                 300
Leu Leu Lys Ala Thr Cys Gly Met Lys Val Ser Ile Pro Thr Lys Ala
305                 310                 315                 320
Leu Glu Leu Lys Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Gly Lys
                325                 330                 335
Pro Ser Ala Phe Glu Pro Ala Thr Glu Met Gln Lys Ser Val Pro Asn
            340                 345                 350
Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile
        355                 360                 365
Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp
    370                 375                 380
Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro
385                 390                 395                 400
Lys Ala Xaa His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu
                405                 410                 415
Gly Ser Pro Val Lys Asp Gly Leu Leu Lys Ala Asn Cys Gly Met Lys
            420                 425                 430
Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe
        435                 440                 445
Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu
    450                 455                 460
Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln
465                 470                 475                 480
Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp
                485                 490                 495
Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser
            500                 505                 510
Gln Lys Asp Val Cys Leu Pro Lys Ala Xaa His Gln Lys Glu Ile Asp
        515                 520                 525
Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp Gly Phe Leu
    530                 535                 540
Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu
545                 550                 555                 560
Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser
                565                 570                 575
Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala
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            580                 585                 590
Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro
        595                 600                 605
Ser Glu Ser Lys Gln Lys Xaa Val Glu Glu Asn Ser Trp Asp Ser Glu
    610                 615                 620
Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala
625                 630                 635                 640
Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser
                645                 650                 655
Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala
            660                 665                 670
Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu
        675                 680                 685
Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala
    690                 695                 700
Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln
705                 710                 715                 720
Glu Leu Cys Ser Val Arg Leu Thr Leu Asn Gln Glu Glu Glu Lys Arg
                725                 730                 735
Arg Asn Ala Asp Ile Leu Asn Glu Lys Ile Arg Glu Glu Leu Gly Arg
            740                 745                 750
Ile Glu Glu Gln His Arg Lys Glu Leu Glu Val Lys Gln Gln Leu Glu
        755                 760                 765
Gln Ala Leu Arg Ile Gln Asp Ile Glu Leu Lys Ser Val Glu Ser Asn
    770                 775                 780
Leu Asn Gln Val Ser His Thr His Glu Asn Glu Asn Tyr Leu Leu His
785                 790                 795                 800
Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys Leu Glu Ile
                805                 810                 815
Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys Tyr Phe Glu
            820                 825                 830
Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln Met Thr Leu
        835                 840                 845
Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln Tyr Ser Gly
    850                 855                 860
Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr Ser Lys Leu
865                 870                 875                 880
Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile Glu Ser His
                885                 890                 895
His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln Ile Val Thr
            900                 905                 910
Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly Asp Ala Cys
        915                 920                 925
Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Ile Tyr Asn Asn
    930                 935                 940
Glu Val Leu His Gln Pro Leu Ser Glu Ala Gln Arg Lys Ser Lys Ser
945                 950                 955                 960
Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp Ala Leu Arg Glu Asn Thr
                965                 970                 975
Leu Val Ser Glu His Ala Gln Arg Asp Gln Arg Glu Thr Gln Cys Gln
            980                 985                 990
Met Lys Glu Ala Glu His Met Tyr Gln Asn Glu Gln Asp Asn Val Asn
        995                 1000                1005
Lys His Thr Glu Gln Gln Glu Ser Leu Asp Gln Lys Leu Phe Gln Leu
    1010                1015                1020
Gln Ser Lys Asn Met Trp Leu Gln Gln Gln Leu Val His Ala His Lys
1025                1030                1035                1040
Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile Asp Ile His Phe Leu Glu
                1045                1050                1055
Arg Lys Met Gln His His Leu Leu Lys Glu Lys Asn Glu Glu Ile Phe
            1060                1065                1070
Asn Tyr Asn Asn His Leu Lys Asn Arg Ile Tyr Gln Tyr Glu Lys Glu
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        1075                1080                1085
Lys Ala Glu Thr Glu Asn Ser
    1090                1095


<210> 494
<211> 743
<212> PRT
<213> Homo sapiens

<220>
<221> variant
<222> (1)...(743)
<223> Xaa = Any amino acid

<400> 494
Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Ser Gln His Cys
                  5                  10                  15
Tyr Ala Gly Ser Gly Cys Pro Leu Leu Glu Asn Val Ile Ser Lys Thr
             20                  25                  30
Ile Asn Pro Gln Val Ser Lys Thr Glu Tyr Lys Glu Leu Leu Gln Glu
         35                  40                  45
Phe Ile Asp Asp Asn Ala Thr Thr Asn Ala Ile Asp Glu Leu Lys Glu
     50                  55                  60
Cys Phe Leu Asn Gln Thr Asp Glu Thr Leu Ser Asn Val Glu Val Phe
 65                  70                  75                  80
Met Gln Leu Ile Tyr Asp Ser Ser Leu Cys Asp Leu Phe Met Ser Pro
                 85                  90                  95
Ala Lys Glu Thr Ser Glu Lys Phe Thr Trp Ala Ala Lys Gly Arg Pro
            100                 105                 110
Arg Lys Ile Ala Trp Glu Lys Lys Glu Thr Pro Val Lys Thr Gly Cys
        115                 120                 125
Val Ala Arg Val Thr Ser Asn Lys Thr Lys Val Leu Glu Lys Gly Arg
    130                 135                 140
Ser Lys Met Ile Ala Cys Pro Thr Lys Glu Ser Ser Thr Lys Ala Ser
145                 150                 155                 160
Ala Asn Asp Gln Arg Phe Pro Ser Glu Ser Lys Gln Glu Glu Asp Glu
                165                 170                 175
Glu Tyr Ser Cys Asp Ser Arg Ser Leu Phe Glu Ser Ser Ala Lys Ile
            180                 185                 190
Gln Val Cys Ile Pro Glu Ser Ile Tyr Gln Lys Val Met Glu Ile Asn
        195                 200                 205
Arg Glu Val Glu Glu Pro Pro Lys Lys Pro Ser Ala Phe Lys Pro Ala
    210                 215                 220
Ile Glu Met Gln Asn Ser Val Pro Asn Lys Ala Phe Glu Leu Lys Asn
225                 230                 235                 240
Glu Gln Thr Leu Arg Ala Asp Pro Met Phe Pro Pro Glu Ser Lys Gln
                245                 250                 255
Lys Asp Tyr Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr
            260                 265                 270
Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His Gln Lys Glu
        275                 280                 285
Ile Asp Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asn Lys Asp Gly
    290                 295                 300
Leu Leu Lys Ala Thr Cys Gly Met Lys Val Ser Ile Pro Thr Lys Ala
305                 310                 315                 320
Leu Glu Leu Lys Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Gly Lys
                325                 330                 335
Pro Ser Ala Phe Glu Pro Ala Thr Glu Met Gln Lys Ser Val Pro Asn
            340                 345                 350
Lys Ala Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Glu Ile
        355                 360                 365
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Leu Pro Ser Glu Ser Lys Gln Lys Asp Tyr Glu Glu Ser Ser Trp Asp
    370                 375                 380
Ser Glu Ser Leu Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro
385                 390                 395                 400
Lys Ala Xaa His Gln Lys Glu Ile Asp Lys Ile Asn Gly Lys Leu Glu
                405                 410                 415
Gly Ser Pro Val Lys Asp Gly Leu Leu Lys Ala Asn Cys Gly Met Lys
            420                 425                 430
Val Ser Ile Pro Thr Lys Ala Leu Glu Leu Met Asp Met Gln Thr Phe
        435                 440                 445
Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala Ile Glu
    450                 455                 460
Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys Asn Glu Gln
465                 470                 475                 480
Thr Leu Arg Ala Asp Glu Ile Leu Pro Ser Glu Ser Lys Gln Lys Asp
                485                 490                 495
Tyr Glu Glu Ser Ser Trp Asp Ser Glu Ser Leu Cys Glu Thr Val Ser
            500                 505                 510
Gln Lys Asp Val Cys Leu Pro Lys Ala Xaa His Gln Lys Glu Ile Asp
        515                 520                 525
Lys Ile Asn Gly Lys Leu Glu Glu Ser Pro Asp Asn Asp Gly Phe Leu
    530                 535                 540
Lys Ala Pro Cys Arg Met Lys Val Ser Ile Pro Thr Lys Ala Leu Glu
545                 550                 555                 560
Leu Met Asp Met Gln Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser
                565                 570                 575
Ala Phe Glu Pro Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala
            580                 585                 590
Leu Glu Leu Lys Asn Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro
        595                 600                 605
Ser Glu Ser Lys Gln Lys Xaa Val Glu Glu Asn Ser Trp Asp Ser Glu
    610                 615                 620
Ser Leu Arg Glu Thr Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala
625                 630                 635                 640
Thr His Gln Lys Glu Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser
                645                 650                 655
Thr Ser Leu Ser Lys Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala
            660                 665                 670
Arg Glu Leu Gln Lys Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu
        675                 680                 685
Gln Met Lys Lys Lys Phe Cys Val Leu Lys Lys Lys Leu Ser Glu Ala
    690                 695                 700
Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln
705                 710                 715                 720
Glu Leu Cys Ser Val Arg Phe Leu Thr Leu Met Lys Met Lys Ile Ile
                725                 730                 735
Ser Tyr Met Lys Ile Ala Cys
            740
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<210> 495
<211> 410
<212> PRT
<213> Homo sapiens

<400> 495

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Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Ser Gln His Cys
                  5                  10                  15
Tyr Ala Gly Ser Gly Cys Pro Leu Leu Glu Asn Val Ile Ser Lys Thr
             20                  25                  30
Ile Asn Pro Gln Val Ser Lys Thr Glu Tyr Lys Glu Leu Leu Gln Glu
         35                  40                  45
```

```
Phe Ile Asp Asp Asn Ala Thr Thr Asn Ala Ile Asp Glu Leu Lys Glu
     50                  55                  60
Cys Phe Leu Asn Gln Thr Asp Glu Thr Leu Ser Asn Val Glu Val Phe
 65                  70                  75                  80
Met Gln Leu Ile Tyr Asp Ser Ser Leu Cys Asp Leu Phe Met Gly Thr
                 85                  90                  95
Arg Ala Leu Gln Cys Glu Val Ser His Thr His Glu Asn Glu Asn Tyr
            100                 105                 110
Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala Met Leu Lys
        115                 120                 125
Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys Glu Asn Lys
    130                 135                 140
Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala Glu Leu Gln
145                 150                 155                 160
Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg Ala Ser Gln
                165                 170                 175
Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr Met Leu Thr
            180                 185                 190
Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu Ala Glu Ile
        195                 200                 205
Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp His Asp Gln
    210                 215                 220
Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His Ile Ala Gly
225                 230                 235                 240
Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser Ser Thr Ile
                245                 250                 255
Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala Gln Arg Lys
            260                 265                 270
Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp Ala Leu Arg
        275                 280                 285
Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln Arg Glu Thr
    290                 295                 300
Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn Glu Gln Asp
305                 310                 315                 320
Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp Gln Lys Leu
                325                 330                 335
Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln Leu Val His
            340                 345                 350
Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile Asp Ile His
        355                 360                 365
Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu Lys Asn Glu
    370                 375                 380
Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile Tyr Gln Tyr
385                 390                 395                 400
Glu Lys Glu Lys Ala Glu Thr Glu Val Ile
                405                 410
```